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THE ADRENAL CORTEX AND ELECTROLYTE METABOLISM*

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Some years ago (Zwemer, 1927) we observed that cats with adrenal insufficiency had "many symptoms that coincided with those of anhydremia. There is a rapid weight loss, the skin becomes gray, dry and wrinkled and loses its elasticity (as shown by the dry neck fold when the animal is picked up); the mucous membranes become dry and lustreless; the extremities are cold, although the rectal temperature may be high."

In a study of the "Pathologic Histology of Adrenalectomized Cats" with Dr. H. E. MacMahon (1929) we reported the fact that "the body is dehydrated, the surfaces of the peritoneal cavity, though smooth, lack their usual sheen. The liver and spleen are moderately congested, and the blood that flows from the freshly cut surfaces is unusually viscid."

"The clinical symptoms of (experimental) adrenal insufficiency include asthenia, anorexia, dehydration with loss of tissue turgor, decreased or stagnated peripheral circulation and early coldness of the extremities" (Zwemer, 1931). Many similar observations have previously and since been made by others.

A concentration of the blood with an increase in blood solids was reported by Gradinescu in 1913 and by Donath in 1914. Kellaway and Cowell (1923), Lucas (1926) and Hartman with his collaborators (1927) have confirmed this blood concentration.

In 1927 Viale and Bruno stated that the blood concentration in dogs is due to loss of plasma and suggested increased vascular permeability as an explanation. A few years later, in studying the relationship of adrenal insufficiency to anaphylactic and histamine shock, Wyman and Tum Suden (1930) found as high as 40 per cent decrease in plasma volume. Very recently, Swingle, Pfiffner, Vars, Bott and Parkins (1933) reported a similar decrease in plasma volume with the familiar increase in hemoglobin and red blood cells and also have correlated this with shock.

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The condition of the entire body, then, seems to be a reflection of the changes in body fluids.

In Addison's original papers, "On the constitution and local effects of disease of the suprarenal capsules," he called the syndrome "Idiopathic Anemia" (1849, 1855). Before being too critical of his classification of the disease we should remember the early connotation of anemia, as a lack of blood as a whole and not simply a deficiency of red blood cells or hemoglobin as we now define the term. He mentions "bloodlessness, extreme prostration and various shades of alteration of the skin," again, "the lips, gums and tongue seem bloodless"; in another instance, "general anemia occurring without any discoverable cause—no previous loss of blood," and in a case report, "these unequivocal signs of feeble circulation." These terms are in exact accord with a forty per cent decrease in the volume of the circulating fluid.

There is a general agreement that a loss of water occurs in adrenal insufficiency, and amelioration of symptoms by administration of fluids has been reported by a number of investigators (Soddu, 1898; Stewart, 1913; Rogoff and Stewart, 1928; Marine and Bauman, 1927; Zwemer, 1925, 1927; Corey, 1927) with varying degrees of success.

In addition to the water loss, studies on the blood chemistry of adrenal insuffiicency showed that certain other constituents decrease per unit volume of blood, in spite of the general concentration.

Our earlier determinations (Zwemer and Sullivan, 1931; Sullivan, MacLean and Zwemer, 1932) confirmed the findings of Marshall and Davis (1916), Bauman and Kurland (1926), Hartman, et al. (1927) and Swingle and Eisenman (1927) in that high NPN, low chloride and low carbon dioxide capacity values were obtained. Further chronological analysis indicated the importance of the CO_2 capacity-decrease in relation to observable symptoms.

Studies on the blood electrolytes were then necessary as it was important to know whether the loss in CO_2 combining power was due to an increase in acid or to a loss of base. In a condition of compensated acidosis there is an excretion of bicarbonate as alveolar CO_2 with release of the basic ion which is then combined with the non-volatile acid until the latter can be excreted. A more uncommon type of reduction in alkaline reserve is that produced by an actual loss of base.

Swingle (1927) says in regard to sodium, "it soon became evident that this substance remained practically unchanged after adrenal extirpation. In general a slight drop in the serum sodium occurred, but the decrease is not of sufficient magnitude to warrant serious consideration. We did not anticipate any change in the sodium content of the blood since the level of this substance is not known to vary greatly in any pathological condition."

Adrenal insufficiency, nevertheless, seems to be the exception. A marked loss of blood sodium occurs after adrenal removal or deficiency according to Bauman and Kurland (1926), Sullivan, MacLean and Zwemer

(1932), Loeb (1932), Loeb, et al. (1933) and Zwemer and Sullivan (1933). We also find a definite decrease in the blood chlorides and a rise in serum potassium.

The significance of the loss of sodium and chloride can be appreciated when we remember that "both Schloss (1912) and Meyer and Cohen (1911) have expressed the view that gain or loss of intrinsic fluid by the body is accompanied by gain or loss of total salts in molar amounts equivalent to those existing in body fluids. Gamble and his co-workers in extensive experiments (1923a, 1923b, 1925, 1928) have shown that a loss of water from the body is followed by a loss of base, and conversely, base depletion of the organism results in water loss." Peters and Van Slyke, in their review of the experimental work, further state that "if the water loss from the body is extra-cellular, the base loss is Na." Both are lost in experimental adrenal insufficiency, although the initiator is not known. Chemically, at least, the syndrome may be directly attributable to a loss of sodium, chloride and extra-cellular water.

That most of the sodium is lost through the kidney is the conclusion of Loeb, et al. (1933) from their electrolyte balance studies on three adrenalectomized dogs. However, we believe that in the diarrhea frequently present in early adrenal insufficiency a great deal of base may be lost by way of the pancreatic juice (cf. Gamble and McIver, 1928). The base from this source also would be lost in severe vomiting. Furthermore, experiments by Zucker, Newberger and Berg (1930) have indicated that "as a secreting gland, the pancreas takes precedence over the kidney in its lien on both water and base." In a personal communication to the writer these authors report a definite prolongation of life in adrenalectomized cats by the oral administration of pancreatic juice. These results may be due solely to the contained base, or may involve additional unknown factors. We believe that drastic relief of constipation in late adrenal insufficiency is to be avoided, as the resultant fluid stools would carry out additional fixed base and chloride and thus further disturb the electrolyte balance with probable fatal consequences.

The loss of chloride from the body becomes important when we remember the anoxemia that is present in adrenal insufficiency (Gradinescu, 1913; Goldzieher, 1933) and the probable rôle of the Cl ion in oxygen transportation. The achlorhydria sometimes found in Addison's disease may be correlated with the chloride loss and the decreased blood bicarbonate.

The rise in blood K also is important. It may indicate an adaptive mechanism to maintain the osmolar pressures in the body fluids by withdrawal of potassium and cellular water from the tissues. Gerard (1912) has shown that glandular, muscle and nervous tissues have a high K/Na ratio. On the other hand, a breakdown of tissues with a release of K or a weakening of that force which for convenience has been called "the differential permeability of the cell membrane" may have occurred. Hastings and Compere (1931) found that the concentration of K in the blood of

dogs dying of adrenal insufficiency was as high as that in dogs dying of KCl poisoning. We have found equally high amounts of blood K in the cat (Zwemer and Sullivan, 1933).

Although the physical and chemical reactions of Na and K are very similar, Na is apparently incapable of being replaced in plasma by K without fatal results. This is probably due to the fact that the cells of the body are adjusted to an electrolyte constant of the fluid media (plasma, lymph and interstitial fluids). McCallum's (1903; 1926) interesting theory attributes our present base proportions to the concentration of sea water at the time our remote ancestors mutated or acquired the mechanism for maintaining their own circulating environment.

Considerable importance has been attached by some investigators—Harrop, et al. (1932)—to the high NPN as a criterion of adrenal insufficiency.

The NPN rise may be due to interference with the base-sparing mechanism of ammonia formation or to the diminishing amount of fluid available for excretion since the kidney does not concentrate nitrogenous metabolites to any great extent. If the concentrating powers of the kidney are impaired, even more fluid is necessary. According to Loeb, et al. (1933), there is a rise in blood NPN during the early insufficiency polyurea. Marshall and Davis (1916), Hartman (1927), Gunn (1928), Marine (1928) and MacMahon and Zwemer (1929) have all reported a fatty metamorphosis of the proximal convoluted tubules of the kidney in adrenal insufficiency. This would interfere with urine concentration and may be a part of the irreversible state (Hartman and Winter, 1933) from which recovery is not possible.

The indication of the significance of sodium and chloride in the syndrome of adrenal insufficiency naturally brings on the question of the effect of treatment on the chloride and sodium ions, and of the possible beneficial effect of treatment with sodium compounds.

Injections of adrenal cortex extract bring about an increase in blood sodium and chloride or prevent the drop that usually occurs (Zwemer and Sullivan, 1933). This sodium retention is reflected in the carbon dioxide rise which we have previously emphasized (Zwemer and Sullivan, 1931; Zwemer, 1931) and which has been found to be true for the normal rabbit by Wenner (1932). The latter confirms our finding that a high normal CO_2 capacity fails to rise after extract.

We have previously mentioned that many investigators have treated the water-loss symptoms with fluids injected or given by mouth. The best of these fluids, as Marine and Bauman (1927) pointed out, have sodium in them. They attribute their failure to obtain good results with hypertonic salt solutions to a lack of water and its diuretic effects. We believe it may have been due to an unusually rapid change in the osmotic pressure and electrolyte balance of the blood.

Recent work by Loeb (1932, 1933) on a patient with Addison's disease, and by the writer on animals, indicates that common salt and other

sodium salts are an effective treatment when given by mouth in adequate amounts. This can be calculated from the difference between their CO_2 capacity and the optimum by the formula of Palmer and Van Slyke (1919). It takes 0.026 grams of $NaHCO_3$ per kilogram of body weight to raise the CO_2 capacity one volume per cent. The human and feline patients voluntarily drink the fluid necessary for the absorption and utilization of the salt in the hydration of their blood and other extra-cellular body fluids. The subsequent ability and inclination to take food may in part be explained by Apperly's (1931) observation that the HCl concentration in the stomach parallels the bicarbonate of the blood. Additional information as to the changes taking place in the blood can be obtained from the work of Harding, Allin and Van Wyck (1924). They state that "an increased concentration of sodium chloride in the blood brought about by increased intake is compensated by an increased blood volume; and that varying inversely with the state of hydration is the concentration of blood uric acid."

The life expectancy of a completely adrenalectomized cat can be definitely extended by the oral administration of salt or other sodium compounds. In a series of ten such animals (Table 1) we had an average survival period of 18.4 days. Even the shortest-lived animal lasted as long as the present average of our controls (ten days), and the best one survived over three times the control period (thirty-five days). We have used NaCl, $NaHCO_3$ and a crude mixture (beef bouillon cubes) of Na glutamate and

TABLE I

THE EFFECT OF SODIUM SALTS BY MOUTH ON THE SURVIVAL OF ADRENALECTOMIZED CATS

Cat No.	Type of Adrenalectomy	Treatment	Survival in Days	Per Cent Loss in Body Weight
P 1	One-stage... (Abdominal)	NaCl 0.5 gm. capsule per day	14	15
P 2	One-stage...	NaCl or $NaHCO_3$ given by capsule	19	21
P 3	One-stage...	$NaHCO_3$ by capsule. Body weight maintained for nine days, then gradual drop to end	35	20
P 4	Two-stage.. (Lumbar)	$NaHCO_3$ by capsule	*12	14
P 5	Two-stage..	NaCl given on food. Cat had a bad temper so could not give capsules as the use of force vitiates the beneficial effects of treatment	14	12
P 6	Two-stage..	$NaHCO_3$ by capsule. Cat had blood in stools and urine..	12	14
P 7	One-stage...	$NaHCO_3$ given by capsule	23	18
P 8	One-stage...	Beef tea concentrate in 0.5 gm. capsules	20	18
P 9	One-stage...	Beef tea concentrate. This cat was infected with round worms and did not always retain its capsules	10	10
P 10	One-stage...	Beef tea concentrate. This cat maintained its pre-operative body weight until eight days before death, then lost it gradually	25	9

*An intracardiac injection of adrenal cortex enabled this cat to recover from coma and live an additional two days on the salt treatment, i.e. 14 days in all.

NaCl. The larger molecular combinations of sodium will probably prove to be the most effective as is the case in the treatment of parathyroid insufficiency with calcium compounds.

An abbreviated protocol (Series P, Cat No. 2) of one of the cats that had a survival period close to the average for the group, gives the essential

CAT P 2

BLACK AND WHITE MALE

		Weight in Kg.
10/25/32	Removed both adrenals at 11:00 A.M.	4.649
	2:30 P.M.—Good recovery, cat drank water.	
10/26–28/32	Gave 0.5 gm. NaCl daily.	
10/29/32	Changed to 0.5 gm. $NaHCO_3$ daily.	4.309
11/ 1/32	Had bad temper so could not give capsule.	
11/ 2/32	Cat in poor condition, so gave 1.5 gms. $NaHCO_3$.	4.195
11/ 3/32	Had taken some food and extremities are again warm (better circulation?)	
11/ 4/32	General condition quite good.	4.110
11/ 5–10/32	Gradual decline.	
11/11/32	Refused food.	3.742
11/13/32	Died on 19th day (average survival for this series, 18.4 days). Had lost 20 per cent of its body weight.	3.686

Post Mortem: Careful search and sectioning of suspicious tissue failed to reveal any accessory adrenal cortical tissue. An unusual condition was the relatively large amount of firm white fat instead of the usual meager amount of yellow fat.

facts of the case. Omission of the salt capsule for even one day brought about an unfavorable reaction which required three times the calculated daily dose to save the animal. This is reminiscent of the effects of withdrawal of cortin and the subsequent need for larger doses. An unusual post mortem finding is the relatively large amount of firm white (hydrated?) fat present. The usual condition after adrenal insufficiency is a meager amount of yellow fat.

In spite of our success in delaying the fatal results of adrenalectomy, we do not believe that sodium chloride is a cure for adrenal cortex insufficiency. In fact, our present evidence would indicate that something (a hormone) is necessary to make the salt and water stay in the body. The condition is similar to severe intestinal intoxication in babies (MacLean, Sullivan and Zwemer, 1932). In these cases large amounts of bicarbonate of soda alleviated the symptoms but did not always effect a cure. The administered base continued to be eliminated unless some adrenal cortex extract was injected. Retention of base followed injection of extract, with a subsequent rise in the CO_2 capacity of the blood and a gain in body weight. The same is true in general of the Addison's disease patients now being treated with salt (Loeb, personal communication); in severe cases there is need of a small amount of hormone to make the salt treatment effective.

However, sodium salts alone are of great benefit and may be instrumental in curing cases of partial insufficiency in which some active corticoadrenal cells are present. In experiments leading to the production of gradual adrenal insufficiency (Zwemer and Lerner) we found that subtotal-adrenalectomy plus traumatization of the remaining third of one adrenal produced eventual death. In the interval between the operation and the

fatal outcome there were alternate periods of apparent good health and typical adrenal insufficiency. One cat so operated upon was given the salt treatment during a period of insufficiency. He made a rapid recovery and gained 20 per cent over his original pre-operative body weight. Temporary omission of salt from his diet, some time ago, produced a mild relapse but for the past three months he has remained in good health.

Experiments now in progress are directed toward the elucidation of a few facts concerning the mechanism of release of the hormone from the adrenal cortex and its action in enabling the body to absorb and retain salt and water.

SUMMARY

1. Calculated amounts of sodium salts by mouth were effective in prolonging the survival period of ten completely adrenalectomized cats to an average of 18.4 days.

2. Experiments leading us to the use of sodium salts are reviewed together with a correlation of the blood chemical and clinical observations.

3. From the results of the experiments here presented, and others now going on, we reaffirm our opinion that the adrenal cortex has a regulative effect on the salt and water metabolism of the cell. Naturally, this effect is most marked in those tissues primarily concerned with movements of fluid into, within and out of the body.

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THE EFFECTS OF SODIUM BROMIDE AND OTHER HALOID SALTS UPON THE WEIGHT AND STRUCTURE OF THE THYROID GLAND IN THE ALBINO RAT

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Investigations on the relations of the halogens to the morphology of the thyroid gland have gradually extended. The work of Marine and Kimball (1917) had apparently led to good understanding of the effects of iodine until more recent work by Loeb (1920) cast doubt upon the validity of some of their conclusions. The relation of the chlorides or calcium to the weight and structure of the thyroid gland, speculated upon by Répin (1908), has never been completely established. Goldemberg (1921) reported changes in the microscopic picture of the thyroid gland as a result of feeding fluorides to experimental animals, but Chaneles (1929) was unable to confirm this finding. It is only within recent years that any studies revealing structural changes caused by the action of bromides on the thyroid gland have been attempted.

It is important to note that most of the workers in this field have confined their activity to an evaluation of the effect of a single one of the halogens. There has been no attempt to correlate the activity of the haloid salts on the morphology of the thyroid gland by concurrent experiments. With this in mind the present study was undertaken.

MATERIALS AND METHODS

Recently weaned and young adult male and female albino rats of the Wistar strain from the colony in the Institute of Anatomy of the University of Minnesota were used. In all, 123 animals were used, including 51 controls and 72 test rats in the various groups. The period during which the rats were under experimental conditions varied from 66 to 123 days.

The controls include two groups, 33 normal stock rats, the age and weight of which approximated that of the test groups, and 18 direct control rats.

The normal stock rats were obtained from the colony animals, which are fed on the following diet (parts by weight): whole ground wheat, 67.5; crude casein, 15.0; whole milk powder, 10.0; butter (unsalted), 5.2; calcium carbonate (U.S.P.), 1.5, and sodium chloride (commercial), 0.8. One per cent cod liver oil (E. L. Patch Co.) is added to this diet before feeding.

The 18 direct control animals were fed on the relatively low-iodine "basal" experimental diet which was composed of the following ingredients (parts by weight): whole ground Minnesota wheat, 85.0; crude

Minnesota casein, 10.0; dried Minnesota spinach, 3.5; calcium carbonate (C.P.), 1.0, and sodium chloride (C.P.), 0.5.

No determination of the iodine content of the basal diet was made. Each of the organic components, however, was chosen for its low iodine content as shown by McClendon (1927). The vitamin content was probably sufficient. Vitamins B and E were supplied by the whole wheat, while the spinach and casein contributed A and D.

The figures for the body weights and thyroid gland weights of 62 12-weeks old stock albino rats from the colony of the Institute of Anatomy of the University of Minnesota reported by Freudenberger (1932) were used to compare with the control series.

The 72 test animals were divided into four groups. Of these, two groups were further divided into sub-groups. Their distribution and diet are indicated in Table I. Where a range is indicated, the amount of each

TABLE I

DATA RELATIVE TO TEST GROUPS OF RATS USED

Test Salt Added to Basal Diet	Percentage of Salt in Diet	Number of Rats on Test	Number of Days of Test	Age of Rats at Start of Test
Sodium Bromide....	0.5–1.0.....	9	51–89.....	Recently weaned
Sodium Bromide....	0.5–0.75.....	16	Killed singly at 5-day intervals after initial 17-day period. Last rats killed after 73 days on test.	3 months
Sodium Bromide + Sodium Iodide....	0.5–1.0.....	5	66.....	3 months
Sodium Chloride....	2.0–3.0.....	9	92–143.....	Recently weaned
Calcium Chloride...	2.0.....	8	71–123.....	Recently weaned
Sodium Iodide.....	0.5–1.0.....	16	66–123.....	9 recently weaned; 7 at 3 months
Sodium Fluoride....	2.0–10.0 mgm. per day	9	71–119.....	Recently weaned

haloid salt given to the experimental animals was determined by their tolerance and nutritional state. The medium of supply was either the food or the water.

Tap water was constantly supplied to all groups by means of bottles with glass siphon outlets.

At the conclusion of the experiment the animals were killed with chloroform. To prevent postmortem changes the thyroid gland, still attached to the trachea and larynx, was removed at once. Dissection of the gland from these structures was carried out immediately. The weight in a closed container was determined to the nearest tenth of a milligram on a chemical balance. Immediately after weighing, the tissue was immersed in the fixing agent.

The fixation method followed was that described by Zirkle (1930) for woody tissue. Following this procedure it was run through four changes of pure paraffin (M.P. 56-58° C.) for twenty minutes each, and was finally embedded therein. Sections were cut at either five or eight microns in thickness. The former were used for more detailed histologic study. The

staining technique with hematoxylin and eosin was that described by Guyer (1917).

The relative thyroid weight ("RTW"), which is used in this paper as the basis for comparison of results, represents the number of milligrams of whole fresh thyroid gland per one hundred grams of body weight. Jackson (1913) and Donaldson (1924) used the percentage of body weight in determining age and sex differences in thyroid weight. McCarrison and Madhava (1932), designate as "r" the ratio between the observed weight of the thyroid gland (or other organs) and the body weight. They have used this figure as the basis for comparison in various groups. A mathematical and experimental justification of this procedure is included in their article. The mean relative thyroid weight for each experimental group and a statistical comparison of the test groups with each of the control groups are found in Table II.

TABLE II

STATISTICAL SUMMARY OF RESULTS

Group	N	C. V.	Mean RTW	Stock Rats Diff. ± S. E.	Diff. / S. E.	P	Direct Control Rats Diff. ± S. E.	Diff. / S. E.	P
Normal Stock	33	18.9	10.38789 ±0.348						
Direct Control	18	21.8	10.25107 ±0.543	0.13682 ±0.645	0.21	0.841			
Freudenberger's	62	21.4	16.16890 ±0.443	5.78101 ±0.563	10.26	0.00000	5.91783 ±0.700	8.44	0.00000
Sodium Bromide (Full test)	9	17.6	17.41380 ±1.805	7.02591 ±1.139	6.16	0.00000	7.16273 ±1.213	5.90	0.00000
Sodium Bromide (Interval killed)	16	....	.....	.....	....	.....	.....	....	.....
Sodium Bromide + Sodium Iodide	5	19.1	14.85034 ±1.425	4.46245 ±1.467	3.04	0.0027	4.59927 ±1.525	3.01	0.0027
Sodium Iodide	16	21.4	12.32317 ±0.681	1.93528 ±0.765	2.52	0.012	2.07210 ±0.872	2.37	0.019
Sodium Fluoride	9	2.3	8.96836 ±0.073	1.49153 ±0.355	3.99	0.00006	1.28271 ±0.547	2.34	0.018
Calcium Chloride	8	3.3	9.00172 ±0.115	1.38617 ±0.366	3.78	0.00032	1.24935 ±0.554	2.25	0.024
Sodium Chloride	9	17.6	11.52929 ±0.719	1.14140 ±0.901	1.26	0.211	0.86318 ±0.798	1.08	0.280

N, number of individuals; C.V., coefficient of variation; RTW, relative thyroid weight; Diff., difference between means; S.E., standard error of difference; P, probability of occurrence in random samples.

The formulae for computing standard errors, standard deviations and coefficients of variation were obtained from Dunn (1929). If the ratio of the difference between two means to the standard error of the difference is three or more, the difference is considered as certainly significant; if the ratio is between two and three, the difference is probably significant, but if the ratio is below two, the difference is statistically insignificant.

RESULTS AND DISCUSSION

1. *Control Rats.* As shown in Table II, the difference between the mean relative thyroid weights of the stock and direct control groups is not statistically significant. However, when these two groups are compared with Freudenberger's series, the differences are apparently statistically significant. The reason for this is not evident, as the rats were of the same strain and from the same colony. Since Freudenberger completed his work, the stock diet has been changed in only one respect, namely, by the addition of cod liver oil. Thompson (1932) was unable to find that 1 per cent cod liver oil (the same amount given to the stock animals of the present series) was protective against the goitrogenic activity of rachitogenic diets. It is probable that the marked variation between Freudenberger's series and the present series is due chiefly to differenes in technique of dissection. The possibility of actual changes in thyroid weight of the colony in such a short time is rather slight.

The histologic picture of the thyroid gland in the normal stock series is similar to that described by Yamashina (1927) for the normal in white rats. Figure 1 shows a typical area. The colloid is plentiful in amount, staining a light to a deep pink with eosin. The peripheral vacuolation of the colloid is variable, being almost entirely absent in some glands and frequent in others. Cells (desquamated or phagocytes?) in the colloid are infrequent. The epithelium is generally low cuboidal. A few follicles are lined with more flattened cells. The follicles present some marked variations in size. Those situated peripherally are generally larger, while those centrally located are smaller. The connective tissue stroma is small in amount. The blood vessels appear normal.

The histologic picture of the thyroid glands in the direct control animals shows individual variations. For convenience, the glands have been divided into "normal" and "abnormal," according to the histologic findings. The typical or "normal" glands are similar, in general, to those of the stock control animals. It is evident that the relatively low iodine content of the basal diet was not sufficient in these rats to cause anything resembling goiter, either in size or structure of the thyroid gland.

The abnormal glands, of which there were two among the 14 direct control glands examined microscopically, show a large central area with degenerated follicles. These present a lack of colloid with extensive desquamation and degeneration of the follicular cells. The basement membrane is apparently unaffected in this process. The area of abnormal cells appears circumscribed but has no definite capsule of connective tissue. The remainder of the gland, including the peripheral region, presents no other deviations from a normal picture. Both the absolute and the relative thyroid weights of these two "abnormal" glands were within normal limits.

2. *Bromide Experiments.* The differences between the mean relative weights of those rats fed with sodium bromide or with sodium bromide plus

sodium iodide, and the two control groups are shown in Table II. The differences appear to be statistically significant, showing thyroid enlargement in the test rats, although the small number of rats in the sodium bromide plus sodium iodide group precludes any absolute statement regarding the goitrogenic activity of the combined salts. The mean relative thyroid weight of the group fed with sodium bromide and killed at five-day intervals was not determined.

The histologic picture of the thyroid glands of the rats fed with sodium bromide for the full test period is striking (Fig. 2). No colloid is present in the follicles save in a few of those peripherally placed. Where

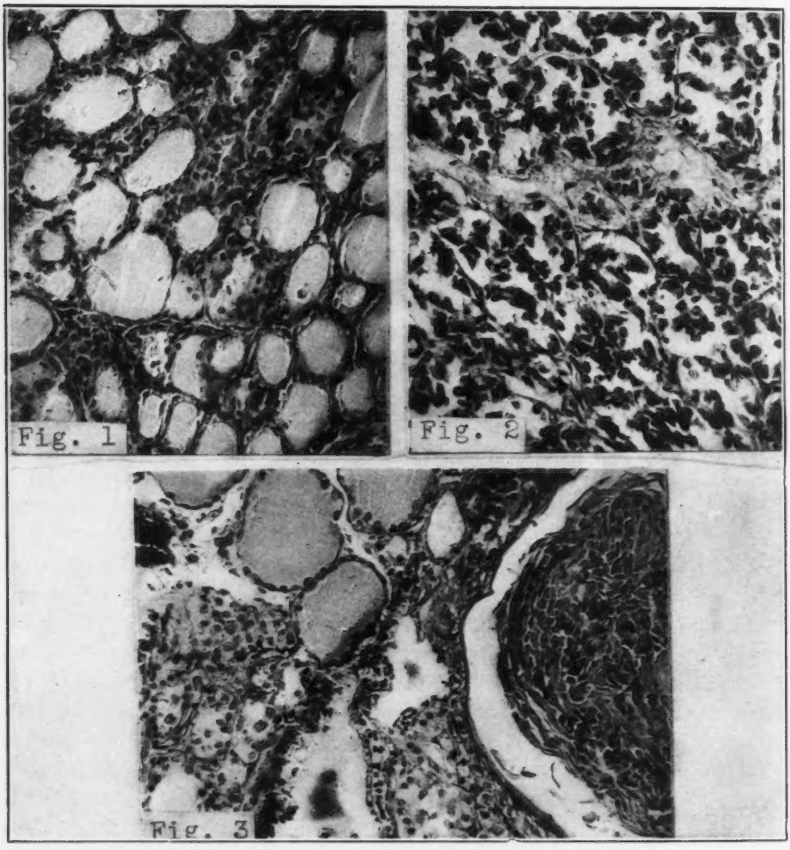

Figure 1. Rat W32-385. Normal stock control. Section showing normal structure of the thyroid gland. Hematoxylin-eosin stain. X 180.

Figure 2. Rat W33-241. Thyroid gland from rat with sodium bromide administered for 89 days. Extreme disintegration and desquamation of the follicular epithelium, loss of colloid and presence of large numbers of intrafollicular cells. Hematoxylin-eosin stain. X 180.

Figure 3. Rat W33-247. Thyroid gland from rat with sodium bromide plus sodium iodide administered for 66 days. Disintegrating follicles characteristic of sodium bromide reaction in lower left, follicles characteristic of sodium iodide reaction in upper left portion of section. Entire right portion of section occupied by a small tumor (leiomyoma?). Hematoxylin-eosin stain. X 180.

colloid is present, peripheral vacuolation is marked. Intra-alveolar (desquamated or phagocytic?) cells are numerous, both in the (apparently) colloid-free and colloid-filled follicles. The colloid present stains a deep shade of pink with eosin. The epithelium varies from low to tall cuboidal or columnar in height. The cytoplasm of many of the cells is vacuolated and the nuclei pyknotic. There is usually extreme desquamation and disintegration of the follicular cells. Although no counts were made, there is an apparent increase in the number of follicles, which are generally smaller than in the normal gland. There is a slight increase in the connective tissue stroma. The blood vessels show a mild to severe hyperemia. The cytologic picture suggests the effect of a toxic factor. Although there can be no direct comparison, these glands apparently closely resemble those described by Cole and Womack (1928) and Leffman (1932) as produced by severe or prolonged infections. Minowada (1928) and more recently, Margolin (1933), have observed the stimulating effect of bromides on the thyroid gland.

A comparison of the histologic pictures of the "abnormal" direct control glands (mentioned above) and the thyroids of the sodium bromide-fed rats suggests that possibly these changes differ in degree only. An explanation of this phenomenon is difficult. Further study is required. It may be due to some goitrogenic factor, inherent in the basal diet, the action of which is accentuated by sodium bromide. The histologic picture of the glands in the rats killed at stated intervals varies in general with the amount of sodium bromide that had been ingested. Definite changes were first noted in the thyroid gland after 42 days on test. The picture in the glands of the rats killed after this time approaches that noted in the full test period animals. The histologic changes apparently precede the increase in weight of the gland, as only those killed after 73 days of test were definitely enlarged.

The histologic picture of the glands of the sodium bromide plus sodium iodide rats presents a combination of that induced by sodium bromide and that found in the animals treated with sodium iodide (Fig. 3). There are found, particularly in the central portions of the glands, follicles filled with colloid and lined with a flat epithelium, intermingled with other follicles which are devoid of colloid and the epithelium of which is desquamated and degenerated. This type of reaction, in which the thyroid gland reacts to the stimuli of two different agents, has already been recorded by Silberberg (1929) for potassium iodide and anterior pituitary lobe extract. A small unidentified tumor resembling a leiomyoma was found in the gland of one of the rats in this group (see Fig. 3).

3. *Sodium Iodide Experiment.* The mean relative thyroid weight for this group when compared with those for the two control groups shows a somewhat doubtful significance ratio (Table II). The thyroid enlargement in this case is probably, but not certainly, significant. The histologic

picture presents a pale staining colloid in which the peripheral vacuoles are rare. Numerous intrafollicular cells are found. A few of the central follicles have only a small amount of colloid but, in general, it is abundant. The epithelium is flattened or low cuboidal, similar to that of a part of the follicles shown in Fig. 3.

4. *Sodium Fluoride Experiment.* In comparison with the mean relative thyroid weights of the two control series, the thyroid glands in this test group are apparently significantly smaller than those of the stock rats and probably significantly smaller than those of the direct control rats (Table II). The reason for this is not apparent. The body weights of six of the rats on this test were low in comparison to the weights of the control animals, perhaps due to malnutrition. This last finding is in agreement with the work of Goldemberg and Chaneles, previously mentioned. Histologically, the glands appear to be normal. The colloid is relatively small in amount and stains a light pink with eosin. Few peripheral vacuoles are present. Intrafollicular cells are infrequent. The epithelium is low cuboidal to flat. The follicles are small. The connective tissue stroma is rather scanty. The blood vessels appear normal. There are no pathologic areas comparable to those found in the "abnormal" direct controls.

5. *Chloride Experiments.* A comparison of the mean relative thyroid weights of the sodium chloride and calcium chloride rats with those of the two control groups is shown in Table II. The sodium chloride rats show no significant difference; but the calcium chloride thyroids appear significantly smaller, especially in comparison with the stock controls. These results are, at this moment, inexplicable. The results of other workers, notably Hellwig (1931) and Hibbard (1933), are not confirmed. However, the diets used by these two workers were very low in iodine content. It is probable that the basal diet employed in this series of experiments surpassed the critical level of iodine content set by Remington (1932). The histologic picture of the glands of both these groups approximated that of the normal. The colloid is pink-staining with eosin. Peripheral vacuolation is infrequent. Intrafollicular cells are rare. The epithelium varies from a low cuboidal to a more flattened type. The follicles are variable in size and generally distended with colloid. The connective tissue stroma is inconspicuous. The blood vessels appear normal.

SUMMARY

Seventy-two young rats were fed a relatively low-iodine basal diet plus small amounts of various halogen salts as follows: sodium bromide, 25 rats; sodium bromide plus sodium iodide, 5; sodium iodide, 16; sodium chloride, 9; calcium chloride, 8; sodium fluoride, 9. For comparison, 18 direct control rats received the basal diet only; 33 stock controls received the normal stock colony diet; and 62 were from Freudenberger's earlier (1932) series on a similar stock diet.

The mean relative thyroid weight was nearly the same in the direct control and stock control groups, but was much lower than in Freudenberger's series, probably due to differences in technique of dissection. In the test groups, the thyroid weight appeared unchanged in the sodium chloride rats, increased on the average 43 per cent in those fed sodium bromide (with or without sodium iodide) or sodium iodide, and decreased 10 per cent in the sodium fluoride and calcium chloride groups.

The histologic structure of the thyroid gland appeared normal in all the control rats, excepting two direct controls in which there was a central area of follicular degeneration. Among the test groups, the sodium fluoride, sodium chloride and calcium chloride rats showed normal thyroid histology. With the sodium iodide, the follicular epithelium was flattened. The most striking changes appeared with sodium bromide, which resulted in a central area of thyroid hyperemia, follicular degeneration, epithelial desquamation and disappearance of colloid. In the group fed both sodium bromide and sodium iodide, the effects of both salts were evident.

I am grateful to Dr. George O. Burr for advice concerning the diets used, to Dr. Edith Boyd for assistance with the statistical methods, and to Dr. C. M. Jackson, under whose direction the investigation was made.

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EFFECTS OF INTERRENAL FUNCTION ON FAT METABOLISM AND TISSUE RESPIRATION*

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The striking effect of adrenal cortical extracts upon the survival of the adrenalectomized animal has caught the general attention to such an extent that other phases of glandular activity pertaining to the cortex have received but little consideration. Yet I emphasized in 1927 (1) that purified extracts of the adrenal cortex which are capable of maintaining life in the adrenalectomized animal also show remarkable effects upon the blood lipoids. Intravenous injection of the active substance is followed by a fall of both cholesterol and phosphatides of the blood. I have continued these investigations during the past six years and was able to show that this drop of lipoids can be produced not only in the rabbit, rat and dog, but also in man. Chart 1 illustrates the effect obtained with three different samples of interrenin on the blood cholesterol of the rabbit. There was an average drop of cholesterol of 14 per cent in the first group, 48.5 per cent in the second, 29 per cent in the third, and a total average of 30.6 per cent. The extent of the drop varied from 6 to 69 per cent. The first two groups consisted of eight rabbits each, the third of seven animals.

Chart 2 shows the effect of interrenin in a series of patients. Three of this group were refractory, but the seven others presented a drop from 14 to 34 per cent with an average of 22.5 per cent.

The active factor which determines the drop of blood lipoids is not resistant to heat and is easily destroyed by boiling. The effect of cortical extracts upon the blood lipoids has been confirmed by several observers (2, 3, 4, 5 and others). These authors agree, however, that there is no quantitative relation between the amount of cortical extract given and the drop of lipoids. Moreover, occasional animals appear to be refractory. I suggested in a previous paper (6) that the fall in lipoids was due to their ingestion by cells of the reticulo-endothelial system which appears to be engorged with lipoid droplets after injection of cortical extracts. Reiss corroborated these observations by demonstrating that the blood cholesterol did not drop in animals which were previously blocked by injection of dyes or india ink. Splenectomy alone did not suffice to prevent the removal of lipoids from the circulation.

Reiss and co-workers (7, 8) used extracts obtained from the interrenal bodies of fish and found them just as effective as those made from mammalian glands. These authors produced potent extracts both by the acid aqueous method and by means of lipoid solvents.

*Read before the Seventeenth Annual Meeting of the Association for the Study of Internal Secretions, Milwaukee, June 12, 1933.

CHART I

BLOOD CHOLESTEROL OF RABBITS IN MGM. PER CENT

Number	Before	After Injection of Interrenin		Maximum Difference	Per Cent.	
		1 Hour	2 Hours			
1	184	160	145	39	21	
2	160	171	150	10	6	
3	140	120	120	20	14	
4	150	150	133	17	11	
5	133	133	100	33	24	
6	181	166	166	21	12	
7	160	150	141	19	12	
8	120	109	102	18	15	Average 14%
9	170	120	90	80	47	
10	120	90	60	60	50	
11	109	88	40	69	62	
12	96	50	40	56	59	
13	126	109	40	86	69	
14	150	111	106	44	30	
15	100	95	60	40	40	
16	160	150	109	51	32	Average 48.5%
17	141	133	100	41	30	
18	125	105	100	25	20	
19	125	105	95	30	24	
20	115	93	90	25	22	
21	83	56	50	33	40	
22	135	104	100	35	25	
23	89	83	53	36	40	Average 29%
24	88	84	88	Boiled interrenin		
25	126	132	120	Boiled interrenin		

CHART II

BLOOD CHOLESTEROL OF PATIENTS IN MGM. PER CENT

Number	Name	Before	After Injection of Interrenin		Maximum Difference	Per Cent.
			1 Hour	2 Hours		
1	H. L.	212	172	162	−50	−24
2	J. M.	118	123	123	+ 5	+ 4
3	S. S.	123	126	126	+ 3	+ 2.5
4	J. S.	126	105	82	−44	−34
5	C. S.	262	226	226	−36	−14
6	S. R.	160	162	160	+ 2	+ 1
7	D. P.	212	153	160	−59	−27
8	S. E.	188	172	163	−25	−14
9	P. T.	320	240	277	−80	−25
10	M. P.	166	135	135	−31	−20

Prolonged administration of cortical extracts is followed by gain in weight of the experimental animal, due to the lipoid fixing (lipopexic) activity of the cortical hormone. This was first observed by Omura (9), and particularly by Reiss, who actually estimated the cholesterol content of the treated animals and found an increase of 30 per cent over that of the controls from the same litter. Feeding of dried adrenal cortex has also increased body weight of the experimental animals (10). These experimental findings were borne out on a series of our patients who were considerably underweight and unable to gain, yet substantially increased their weight during prolonged treatment with the standardized Interrenin solution. Hoskins and Freeman (11) recently reported significant gains in weight of their schizophrenic patients which were obtained by oral administration of cortical extracts.

A rôle of the adrenal cortex in fat metabolism was suggested by the rise in blood cholesterol following removal of the adrenals (12, 13, 14, 15, 16, 17). Thus a lack of cortical hormone is followed by an excess of cholesterol in the blood, just the reverse of what happens after intravenous injection of the hormone. Another important fact is the hypertrophy of the cortex in vitamin deficiencies in which the blood lipoids rise significantly (McCarrison, 18, and others). As Schmitz, et al., have shown (3), both the increase of blood lipoids and the hypertrophy of the cortex can be prevented by injections of cortical extracts. Schmitz used two different cortical preparations: Interrenin prepared by acid aqueous extraction according to my specification (19) and another alkaline extract. Injection of the former produced a drop of both cholesterol and phosphatides, whereas the alkaline extract had no effect upon the phosphatides, although it decreased the blood cholesterol. It seems logical to attribute cortical hypertrophy in these vitamin experiments to a compensatory effort of the gland which expresses an attempt to cope with hypercholesterolemia.

Obesity concomitant with pathological hyperfunction of the adrenal cortex is another indication of the rôle which the cortex plays in the regulation of fat metabolism. Numerous case reports are on record in which a cortical tumor was present accompanied by symptoms of precocious sexual development or virilism. Careful perusal of these reports reveals the presence of obesity as another constant symptom. Some of these subjects were operated upon and afterwards observed for a sufficient length of time to permit the study of the therapeutic result. These reports (20, 21, 22, 23, 24, 25, 26, 27, 28, and others) mention recession of obesity together with improvement of the other symptoms.

It seems that obesity occurs not only in case of tumors of the adrenal cortex but also associated with simple hyperplasia of the gland. Two years ago we described (29) the case of a young girl who showed the clinical picture of adrenal obesity. She weighed 330 pounds at the time of the operation. Within little more than one year after removal of one of her considerably enlarged adrenals, her weight had dropped 140 pounds to a

mere 190. The same operation has been performed since that time on three other patients. They were all young females. One death was due to cardiac failure shortly after operation. Two made an uneventful recovery with the following result: One patient, whose preoperative weight was 168 pounds and who was constantly gaining, lost 19 pounds and kept that weight steadily without any diet or medication. The other patient did not sustain any appreciable loss of weight but her previously rapid gaining was also successfully checked. These cases are to be reported elsewhere in detail with a discussion of the diagnosis of adrenal obesity.

Unilateral adrenalectomy, with apparently satisfactory results, was reported recently in three cases of cortical hyperplasia by Broster and Gardiner-Hill.

Obesity concomitant with cortical hyperfunction gains significance if compared with the extreme loss of fat which prevails in Addison's disease. Many observers have noted, moreover, that the beneficial effect of cortical extract in Addison's disease manifests itself also by a rapid gain in weight (31). We have kept two patients who have had Addison's disease for the past 18 months on treatment with Interrenin and obtained a remarkable gain in weight as one of the signs of successful organotherapy. Adrenalectomized animals also lose weight very rapidly and show complete disappearance of their subcutaneous fat depots at death. They promptly gain weight if put on treatment with cortical extracts.

Summarizing the experimental and clinical evidence, it seems that the adrenal cortex is instrumental in the regulation of fat metabolism. The ability of the cortical hormone to fix the fats in the tissues deserves further investigation.

Another phase of cortical function is related to the utilization of oxygen in the tissues. Bornstein and Holm (32) showed that hyperventilation of the lung sets in after bilateral adrenalectomy. Kuehl (33) administered saline extracts of cortical tissue to adrenalectomized animals and succeeded in relieving their respiratory embarrassment. Marti (34) demonstrated the great sensitivity of adrenalectomized animals to the lack of oxygen. Vincent and Thompson (35) showed failure of respiration in the decerebrated cat after adrenalectomy, and Reiss (36), although disagreeing with the interpretation of these authors, confirmed the fact that respiration could be relieved by administration of cortical extracts.

I have repeatedly called attention to the air hunger and rapid respiration which occurs in the newborn following destruction of the adrenals by hemorrhage (37, 38). In two cases the respiratory embarrassment was relieved by intravenous administration of Interrenin.

Further evidence is contributed by experiments in which animals were poisoned with repeated small doses of cyanide (39). These animals showed a rise in blood cholesterol and a hypertrophy of the cortex quite comparable to the compensatory hypertrophy of the vitamin deficient animals.

The work of Szent-Györgyi (40), Karrer (41), Harris (42) and others has focused interest upon the presence of hexuronic or ascorbic acid in the adrenal cortex. This substance which is supposed to be identical with vitamin C, is one of the strongest biological oxydizing agents. It seems logical to connect the rôle of the cortex in tissue respiration with the unparalleled abundance of ascorbic acid in this gland. However, ascorbic acid is not the life-maintaining factor of the cortex, according to Szent-Györgyi. Its relation to the cortical hormone or hormones requires further studies.

The rôle of the adrenal cortex in the utilization of oxygen is further corroborated by anatomical observations in the fetus and newborn child. It is known that the adrenal glands of the newborn are very large. Their average weight is 4.7 grams in the male and 5 grams in the female. Their

Figure 1. Adrenal gland of infant 21 days of age. Hyperemia of reticular zone; absence of involution. (Low power.)

size is about one-third that of the kidneys, whereas the size of these two organs compares as 1:30 in the adult. The total body weight increases about twenty-fold in adult life, whereas the adrenals just about double their size and eventually reach the average weight of 10.2 grams in the male and 10.6 grams in the female (43). The relatively large weight of the adrenal in the newborn is exclusively due to the overabundance of the cortex, while the medulla is quite scanty at birth.

It is also well known that involution of the cortex sets in immediately after birth (44, 45 and 46). Scammon (47) showed that the loss is greatest within the first week after birth and amounts to about one-third of the total weight. Involution progresses at a lower rate up to the end of the second month when the lowest level is reached which corresponds to about one-half of that at birth. Scammon's curve is based on 1087 measure-

ments of both adrenals in 425 fetuses, 338 newborn and 324 children between the ages of two days and one year.

The decrease in weight of the adrenals is brought about by disintegration of the inner layers of the cortex. The bulk of the cortical tissue succumbs to degenerative changes and gradual resorption. The empty meshes of the stroma are left behind and gradually transform themselves into a fibrillar capsule which surrounds the slowly expanding medulla. This capsule persists for years and is gradually replaced by newly formed cortical tissue.

It was necessary briefly to recapitulate these facts in order to stress the importance of observations which we made on the adrenals of infants born with congenital malformation of the heart. Among several cases

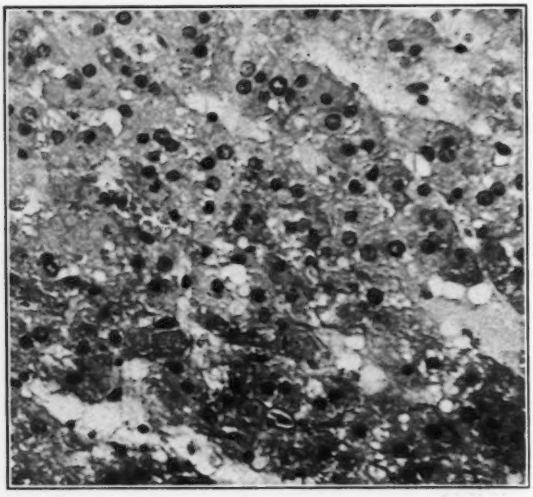

Figure 2. Unimpaired structure of reticular zone. (High power.)

which I have recently examined, three stand out because the infants lived for 21, 6 and 5 days, respectively. Transposition of the arterial vessels and a large defect of the septum were present in all three cases, as a consequence of which only little blood passed through the pulmonary circuit. Cyanosis of these infants was commensurate.

The adrenal glands of these children were comparable in size and weight to those of the newborn. Histological examination also failed to show any physiological involution, although even the youngest of these children should have suffered a loss of close to one-third of its cortex. Yet, the weight of the gland was not reduced even in the 21-day-old child and the microscopical structure of the newborn adrenal still prevailed.

I am fully aware that three cases are not enough to substantiate far-reaching conclusions, yet the rarity of this material enhances its importance. Adrenals of infants with congenital malformation of the heart at

this particular age are not frequently obtained for study. Children with minor malformations usually live on to a time in which subsequent development of the adrenals obliterates evidence of physiological involution. In severe cases of malformation the subjects mostly die immediately after birth, so that there is no time for the onset of involution. These three subjects, however, lived long enough to start involution and the fact that they did not show any indicates that this physiological process is absent or inordinately delayed in congenital malformation of the heart with inadequate aeration and oxydation of the blood.

It is difficult to interpret these observations as long as we fail to account for the excessive size of the cortex in the fetus and its sudden disintegration upon birth. We have called attention before to the relation between cortical function and tissue respiration (38), which would explain the overabundance of the cortex in the fetus. The arterial blood of the fetus is saturated only to 63 per cent with oxygen as compared with 95 per cent of the maternal blood. The oxygen tension in the fetal blood is equal to only 40 mm. mercury as compared to a tension of 100 mm. in the alveoli of the breathing lung (48). Haselhorst and Stromberger (49) calculated even lower degrees of oxygen saturation. This would call for some compensatory mechanism by means of which the fetal tissues could obtain an adequate oxygen supply. Several such adjustments are demonstrable in the fetus: one is the increase in blood volume and in the number of red cells; another, according to Anselmino and Hoffmann (50), is the increased glutathione content of the blood. These authors also claim that dissociation of oxygen is considerably increased in the fetal blood and is quite comparable to that of people living in high altitudes.

The adaptation of the fetus to the dearth of oxygen expresses itself in the ability to utilize 75 per cent of the oxygen available, whereas the maternal tissues utilize only 31 per cent (49). This remarkable difference is suggestive of some factor which is present in the fetus, but disappears after birth. The suggestion is offered that this factor is the accentuated function of the adrenal cortex which is morphologically expressed by its excessive bulk. Onset of pulmonary respiration at birth yields a sudden increase of the oxygen supply and the excess function of the cortex becomes unnecessary. If it is true that the large fetal adrenal provides for proper utilization of oxygen and if the physiological involution of the cortex is a response to the onset of respiration, involution should not occur or be delayed in case the oxygen supply does not materially increase upon birth. This postulate is fulfilled by the absence of involution in three cases of congenital malformation of the heart with excessive cyanosis described in this report.

SUMMARY

Injection of cortical hormone in 23 rabbits elicited a 30.6 per cent (average) drop of blood cholesterol; in 10 men the average drop was 22.5

per cent. The potency of the cortical extracts was found to be destroyed by heating.

Evidence is cited from the literature that the drop of blood cholesterol and other lipoids is brought about through the activity of the reticuloendothelial cells with subsequent storage and fixation of the lipoids in the tissues. Personal observations and data from the literature are quoted which show that prolonged administration of cortical extracts is followed by gain in weight of the patient or experimental animal. Cortical function in fat metabolism is illustrated by a survey of experimental and clinical observations which reveal a loss of weight after adrenalectomy or in Addison's disease and a gain in case of hyperplasia or tumors of the cortex.

Attention is called to the rôle of cortical function in the utilization of oxygen as demonstrated by the respiratory disturbances which follow adrenalectomy or destruction of the adrenals by hemorrhage in children. The excessive size of the fetal adrenal is interpreted as an adaptation to the low oxygen tension of the fetal blood and physiological involution of the cortex after birth as a response to the increased oxygen supply.

Three cases of cardiac malformation in infants are reported in which physiological involution of the cortex failed to occur. Persistence of the fetal cortex in these cases points to the dependence of involution upon increased oxygen supply by pulmonary respiration and suggests active participation in the utilization of oxygen as one of the functions of the adrenal cortex.

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SECRETIN: ITS INFLUENCE ON THE AMOUNT OF HEMOGLOBIN IN THE CIRCULATING BLOOD

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Various investigators (Downs and Eddy, 1; King, 2) have reported an increase in the corpuscle count of the circulating blood after the injection of a secretin preparation. However, as far as we are aware the hemoglobin content has not been determined under these circumstances. The present report embodies results of experiments on rabbits which seem to show that secretin injections increase the hemoglobin in the blood stream.

Two different extracts were used. The first was prepared from the intestine of the dog by the ApH 1802 method of Ivy, Kloster, Luett and Drewyer (3), the significant results of which are shown in Table I. The

TABLE I (6)

DATA OBTAINED FROM READINGS ON THE HEMOGLOBINOMETER AFTER THE INJECTION OF 24 RABBITS WITH SECRETIN PREPARATION ApH 1802

Minutes After Injection	Mean ± Standard Error	Range	Standard Deviation
0 (before injection)	70.7±1.26	59.6−80.2	±6.177
20*	70.5±1.42	56.6−80.2	±6.78
45*	73.1±1.28	58.8−83.2	±6.13
80	73.4±1.56	56.0−83.0	±7.65

*23 determinations made.

method was followed to the point where a powder was obtained, containing both secretin and cholecystokinin, in the proportion of three or four doses of secretin to one of cholecystokinin. The second was a secretin concentrate prepared from the intestine of the hog following the method of Ivy, Kloster, Drewyer and Luett (4), the results of which are shown in Table II.

Rabbits were used in both cases since Lamson (5) reports that adrenaline, fright, pain, etc., cause sudden and marked increase in the red cor-

TABLE II (6)

DATA OBTAINED FROM READINGS ON THE HEMOGLOBINOMETER AFTER THE INJECTION OF 6 RABBITS WITH SECRETIN CONCENTRATE

Minutes After Injection	Mean ± Standard Error	Range	Standard Deviation
0 (before injection)	64.7±1.33	60−67	±3.27
20	66.3±1.33	61−70	±3.26
45	68.2±1.38	64−72	±3.37
80	64.7± .96	62−67	±2.34

puscles of the dog and cat but that these agents are without effect on the erythrocyte count of the rabbit.

A saturated solution of the dried powder was made in 0.9 per cent sodium chloride solution. One cubic centimeter of this solution per kilogram body weight was injected subcutaneously as this was shown to be the most efficient dose (1). Specimens of blood were taken from the ear of the rabbit before the injection and at intervals of 20, 45, and 80 minutes after the injection.

The determinations were made with the Fleischl-Miescher hemoglobinometer. As the rabbits were a mixed lot when delivered to the laboratory there is considerable variation in the hemoglobin findings, many of which are below the normal, which we have found for the average rabbit on a suitable dietary.

In order to establish whether there were significant changes after the injection of the ApH 1802 preparation and of Secretin Concentrate, Fisher's "t" method (6) had to be used. Mean changes and the criteria of significance are tabulated below.

TABLE III

MEAN CHANGES AND THEIR SIGNIFICANCE

(24 rabbits injected with ApH 1802 preparation, and 6 rabbits injected with secretin concentrate)

Minutes After Injection		Mean Change	Criterion of Significance Fisher's "t"	Probability of Difference as Great or Greater Arising From Chance
20	ApH 1802	+0.2	.300	.70 Insignificant
	Secretin Concentrate	+1.67	3.38	< .02 Significant
45	ApH 1802	+2.02	3.02	< .01 Significant
	Secretin	+3.50	8.18	< .01 Significant
80	ApH 1802	+2.71	3.76	< .01 Significant
	Secretin Concentrate	0	0	1. Insignificant

It can be seen that the ApH 1802 acts much more slowly than secretin concentrate but its effect lasts longer. Thus after 20 minutes ApH 1802 had not caused any significant increase while secretin concentrate had. On the other hand, after 80 minues ApH 1802 reached on an average its maximum effect while secretin had lost its effect entirely. It should be mentioned also that the effect of secretin concentrate seems to be more consistent while ApH 1802 shows considerable variation in individual response.

TABLE IV

MAXIMUM CHANGES IN TERMS OF PER CENT

	Range		Mean Per Cent
	From Per Cent	To Per Cent	
ApH 1802	−2.3	+11.7	5.8
Secretin Concentrate	+3.0	+ 7.4	5.4

SUMMARY

(1) Twenty-four rabbits were injected subcutaneously with a secretin preparation (ApH 1802) and six rabbits with a secretin concentrate preparation. The hemoglobin of a unit volume of the circulating blood was determined before the injection, and at intervals of 20, 45, and 80 minutes after the injection.

(2) The mean maximum percentage increase in the first group was 5.8, and in the second group 5.4.

(3) The ApH 1802 preparation appeared to act more slowly than the secretin concentrate but its effect lasted longer.

(4) More consistent results were obtained with the secretin concentrate than with the ApH 1802 preparation.

I am indebted to Mr. E. M. Jellinek and Brother R. Philip for assistance with the statistical data.

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ANTERIOR PITUITARY HORMONE AND TUMOR GROWTH

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Of the numerous hormones said to be elaborated by the anterior pituitary lobe the growth hormone and the gonadotropic sex hormone or prolan have been investigated most thoroughly and their existence is well established. While it is generally assumed that the growth hormone is produced by the eosinophilic pituitary cells and the gonadotropic hormone by the basophilic cells, nothing is known about the site of production of the remaining hormones such as the thyreotropic hormone and the hormones concerned with metabolism. Whether part of the assumed hormonal anterior pituitary action will have to be attributed to the activity of the hypothalamic centers of the autonomic nervous system situated in the neighborhood of the pituitary, is an open question. Functional relations at least between the hypophysis and subthalamic region have been shown to be very probable (Falta, 1; Berblinger, 2).

The literature on the biological action of the anterior pituitary hormones has been the subject of several recent publications: Evans (3), Zondek (4), Aschheim (5), Berblinger (6), Bugbee (7). It is not intended, therefore, to attempt here a further survey of this very wide field of research but to refer briefly to the works of previous investigators which are specially relevant to the study described in this paper.

It seems well established that the gonadotropic hormone or prolan secreted by the anterior pituitary lobe controls the ovarian cycle and induces folliculation and luteinization. Whether prolan is one hormone producing these two processes or whether it consists of two hormones, one (A) inducing folliculation, the other (B) inducing luteinization, is not yet certain though considerable evidence is offered in favor of two hormones (Zondek, Aschheim, Evans). Whether the substance present in the urine of pregnant women and having the same physiological effect on ovarian functions is identical with the gonadotropic hormone or not is still under discussion. Aschheim (5), in his latest edition, defines it as follows: "Gonadotropic substance of the effect and character of the anterior pituitary sex hormone."

It has been definitely shown that while the urine of normal women contains only very small amounts of this substance or hormone—about 5 mouse units per litre—there develops a great increase up to 5,000 units and more during pregnancy. The Aschheim-Zondek test is based upon this fact.

The increased secretion of prolan or of a prolan-like substance in amounts exceeding that found in pregnancy was demonstrated by Zondek

in the urine of women with tumors following pregnancy, such as hydatiform moles and chorion-epithelioma. It is also present, but to a lesser extent—100 to 150 mouse units—in the urine of 80 per cent of women with genital tumors and 36 per cent of extragenital tumors according to Zondek. Ferguson (8) was able to obtain a positive prolan A reaction with the urine of all of the 117 cases of teratoma testis which he examined, except those with established clinical cure after irradiation.

Our object was to study the pathogenesis of prolan excretion in individuals with tumors of various origins and to attempt to explain the relationship between anterior pituitary hormone and tumor growth.

TECHNIQUE

Aschheim-Zondek's technique was closely followed. White female infant mice 6-8 grams in weight and 3-5 weeks of age were used throughout these experiments. Freshly voided morning specimens of urine were made slightly acid to litmus and filtered. The urine then was detoxified by Zondek's ether-sugar method and 3 cc. injected into the mice within 100 hours. They were autopsied 100 hours after the first injection. If ovarian changes such as folliculation, follicular hemorrhage, or luteinization were not readily recognized with the naked eye or with the small power lens after placing the ovaries in glycerin, the ovaries were fixed and sections cut for microscopic study.

As with this method the presence of less than 333 mouse units cannot be detected, Zondek's concentration method frequently was used: the hormone is precipitated with alcohol, washed with ether and taken up in water. A concentration of 1:5 was made. By this method the hormone content of 60 cc. of urine is concentrated to 12 cc. A positive reaction is obtained by injection of 3 cc. if a minimum of 66 mouse units is excreted per litre of urine.

RESULTS

	Native	Concentrated 1:5
I. Genital Tumors		
A. Malignant:		
1. Adenocarcinoma ovari	Pos. Prolan A and B	
2. Carcinoma vaginae	Pos. Prolan A	Pos. Prolan A
3. Carcinoma cervicis		Pos. Prolan A
4. Carcinoma vaginae		Neg.
5. Tumor testis		Pos. Prolan A
(Courtesy Dr. J. S. Eisenstaedt)		
B. Benign:		
1. Cystoma ovari	Neg.	Neg.
2. Fibroid	Neg.	Pos. Prolan A
3. Fibroid	Neg.	
4. Cystoma ovari		Pos. Prolan A
5. Dermoid ovari		Pos. Prolan A
6. Fibroid		Neg.

II. Extragenital Tumors
(Courtesy Dr. Wm. Buchbinder,
Cook County Hospital: No. 1-6.)

1. Carcinoma pancreas	Neg.
2. Carcinoma stomach	Neg.
3. Carcinoma lung	Neg.
4. Carcinoma esophagus	Neg.
5. Carcinoma lung	Neg.
6. Carcinoma lung	Neg.
7. Carcinoma metast. breast. Neg.	
8. Carcinoma breast, extensive. Neg.	
9. Carcinoma recti	Neg.

In this group of cases, increased excretion of the follicle-ripening hormone (Prolan A) was found to be present in four of five patients with malignant genital tumors (the negative case was a vaginal carcinoma), while the luteinization hormone (Prolan B) was found to be excreted in but one case which was of adenocarcinoma of the ovary. Increased secretion of the follicle-ripening hormone was observed in three of six patients with benign genital tumors. In all nine patients with extragenital malignant tumors no increased excretion of anterior pituitary sex hormone could be demonstrated.

DISCUSSION

The question arises as to how the striking increase in the prolan excretion in patients with genital tumors can be explained.

Zondek and Hartoch (9) are inclined to believe that this is due to a specific reactive defense mechanism of the body against the tumorous growth. They believe that the growing tumor exerts a stimulating influence upon the anterior pituitary in favor of increased elaboration of prolan which in turn checks the process of the tumorous growth (Zondek's peripheral theory). In order to substantiate the assumed inhibiting influence of prolan upon tumor growth Zondek and Hartoch injected massive doses of prolan into tumor-bearing mice and obtained a marked retardation of the tumorous growth. In another series of animals it could be demonstrated that the administration of prolan reduces the growth energy of a tumor to such an extent that in the second animal passage the tumor grows only slightly or not at all. They further report improvement in human cancer patients after intravenous injections of large doses of prolan.

In order to support, furthermore, the assumption that it is the process of tumorous growth that stimulates the production of the pituitary sex hormone, the same authors report their clinical observations in acromegaly. In this condition the growth hormone is presumably produced in large quantities and at the same time follicular maturation is inhibited. Increased production of growth hormone, therefore, seems capable of inhibiting the elaboration of the follicle-ripening sex hormone. The authors

surmise that increased production of the sex hormone might inhibit the process of growth. That growth hormone and sex hormone apparently are opposed in their action is also expressed by Evans.

In acromegaly, as stated above, an oppression of the pituitary sex hormone production must be expected. In six cases of acromegaly Watts (10) was unable to demonstrate the pituitary sex hormone in the urine or blood by the injection of as much as 24 cc. of urine or 7.5 cc. of blood serum into rats. In the author's case of acromegaly with complete loss of sexual desire, injection of as much as 10 cc. of the concentrated hormone failed to produce any ovarian changes in the infantile mouse.

Contrary to these findings increased prolan excretion in four of six cases of acromegaly is reported by Becht and Miklos (11). Love (12) also reports a similar finding. This is explained by Berblinger as a compensatory temporary hypertrophy of the prolan-elaborating basophilic cells which he noted histologically. In acromegaly an increase in function and number of the growth hormone-producing acidophilic cells apparently takes place with a proportionate gradual decrease of the prolan-producing basophilic cells. The presence in acromegaly of an eosinophilic pituitary adenoma with compression and gradual destruction of the remaining epithelial pituitary tissue has long been known to occur.

The writer raises the question as to whether the demonstration of the piutitary sex hormone in such cases, or, in other words, the demonstration of still functioning basophilic pituitary epithelium might be valuably utilized as to prognosis and possibly therapy of such cases of acromegaly.

Cushing (13), in his monograph on pituitary basophilism, raises the question: "If the sex maturing principle is excreted by the basophilic cells, should it not be found in the urine of patients with basophilic adenoma?"

Perhaps a consideration of normal physiological conditions might be of value in the understanding of the pathological relations between anterior pituitary and tumor growth.

In the urine of newborns during the first few days of life there is a marked anterior pituitary sex hormone excretion. According to Neumann and Peter (14), this very probably is of maternal origin and accounts for the swelling and hyperemia of genital organs and breast so frequently seen during the first days of life. A similar opinion is expressed by Cutler and Cheatle (15).

In childhood, during the period of normal growth, while the growth hormone is active, there is no biological or clinical evidence of activity on the part of the sex maturing hormone. Schörcher (16) examined the urine of 47 children of different ages; 25 were males and 22 females, some normal, others hospital patients. In none was a positive pituitary sex hormone reaction obtained.

Fully established sexual maturity terminates the period of childhood and usually introduces the onset of termination of physiological growth.

This might be expressed in terms of endocrinology: Full activity of the sex maturing hormone inhibits the activity of the growth hormone. Thus the opposite action of both hormones and the inhibiting influence of the sex hormone upon physiological growth is seen again.

If these statements hold true the increased production of the sex hormone in tumorous growth might indeed be considered to be due to a reactive response to inhibit the process of pathological growth.

This assumption, however, tempting as it may be, cannot be supported by the facts at hand and by our findings. It seems evident that the increased prolan excretion cannot at present be considered as a general reaction to the presence of malignancy per se but more probably as that malignancy involving certain tissues.

The reason why tumors of the genital region particularly influence the prolan excretion may perhaps be found in the fact that although the pituitary regulates the functional activity of the sex glands, the latter are also capable of influencing the pituitary. For a long time it has been known that castration produces definite changes in the anterior pituitary (Tandler and Gross, 17). It was shown by Zondek that castration produced an increased excretion of prolan not only in women but even in men, and the same is true in the stage of functional involution of the menopause.

It may readily be understood, therefore, that tumors of the genital tract situated within or adjacent to the sex glands are capable of influencing the pituitary. This seems all the more probable since not only gross anatomical lesions of the sex glands, but also, as has been shown by Hirsch-Hoffmann (18), delicate functional disturbances as they appear in certain endocrine disorders give rise to an increased prolan excretion. Kraus (19) has found increased prolan excretion in 60 per cent of the patients with cerebral tumors, which he explains as being due to the increased intracranial pressure exerting a stimulating influence upon the pituitary. Attention might be called to this phenomenon as to diagnostic possibilities in questionable cases of cerebral tumors.

The author wishes to express his indebtedness to Dr. Max Cutler, Director of the Tumor Clinic of the Michael Reese Hospital.

SUMMARY AND CONCLUSIONS

1. Anterior pituitary sex hormone excretion was studied in a number of genital and extragenital tumors (mouse test).

2. The relations between anterior pituitary hormone and tumor growth are reviewed and discussed.

3. In four of five cases of malignant genital tumors, increased excretion of the follicle-ripening hormone (prolan A) was demonstrated and in one case of adenocarcinoma of the ovary also the luteinizing hormone (prolan B).

4. In three of six cases of benign genital tumors, increased excretion of prolan A was observed.

5. In nine cases of extragenital malignant tumors, no increased excretion of prolan was found.

6. The increased prolan excretion, frequently found in cases of genital tumors, is explained on the basis of the mutual relationship between anterior pituitary and sex glands.

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EXPERIMENTAL COLLOID GOITER*

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Systematic comparative studies of goiters from different localities have shown that in mountainous regions with severe endemicity most goiters are composed of small acini and are poor in colloid, whereas in level regions the most common type is the colloid goiter. Only in those areas where the diffuse and nodular colloid goiter prevails, does one meet frequently with hyperthyroidism and Graves' disease, while the goiter in mountainous regions is more often associated with a deficient thyroid function.

Marine (10) has pointed out that colloid goiter does not develop from a normal gland by distension of the follicles with colloid, but that the thyroid enlargement is always initiated as an active hypertrophy and hyperplasia. He regards colloid goiter as an involutional stage of hyperplastic goiter.

Marine's view is not supported by my own histologic studies of human goiter. In surgical and autopsy material obtained in Kansas, I have never seen the small-follicular, colloid-poor parenchymatous goiter, the prototype of adolescent goiter in mountainous regions. I am therefore led to believe that in North America and other level countries, the thyroid reacts to the goiter agent with dilatation of the acini due to increased secretion of colloid and that the colloid goiter develops as a rule directly from the normal thyroid gland.

Since goiters vary widely in structure and functional disturbance, according to their geographic extraction, it does not seem likely that the goiters of mountains and lowlands are both caused by the same factor. While iodine deficiency seems to play some rôle in the etiology of the colloid-poor mountain type of goiter, the colloid-rich, large-follicular goiter of level regions cannot be explained by lack of iodine.

In experiments during 1929 and 1932 (2, 3) I was unable to produce hyperplasia of the thyroid in white rats by an almost iodine-free diet. It was concluded that iodine-deficiency by itself cannot be the essential cause of endemic goiter and that there must be rather a positive goitrogenic agent. My negative results were confirmed in a non-endemic region by Hibbard (4), and in a goitrous district by Jackson and P'An (5). In a recent paper, Kenyon (6) objected to our conclusions and pointed out that they are not supported by the successful attempts by Levine (8), Remington (12), Krauss and Monroe (7), Hayden, Wenner and Rucker (1), who reported diffuse hyperplasia of the thyroid occurring in white rats kept on

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a diet containing an insufficient amount of iodine. However, all these investigators used in their experiments just the same positive goiter-causing agent with which I was successful in producing diffuse hyperplasia in 1929, namely, excess of calcium in the food.

The object of the study on which this paper is based was to determine whether goiters produced by the same goitrogenic positive factor, vary in structure when iodine is added to the goitrogenic diet in low, medium and high amount. It was hoped that these observations might furnish a basis for the understanding of the differences in structure and function between the mountain and lowland types of goiter.

EXPERIMENTAL STUDY

The experiments were begun on December 1, 1932, with 40 white rats. Only male animals were used, to exclude any influences of sexual activity on the thyroid gland. The rats were all about 10 weeks old and were approximately the same weight. The 40 animals were divided into four groups, 10 in each, and kept in separate Dormer cages, with floors of mesh wire. No hay or other material was used for bedding. The cages were in a well lighted room, in which the temperature was held constantly at 20° C. In this way possible structural changes of the thyroid, caused by low temperature and darkness, were avoided.

The basal diet was the same for all animals and consisted of cornmeal (50 per cent) and rolled oats (50 per cent), boiled in distilled water. The first group of animals received this food freshly prepared every day, without any other accessories except 100 cc. of distilled water. To the second series of white rats, 100 cc. of 2 per cent calcium chloride was given together with the basal ration.

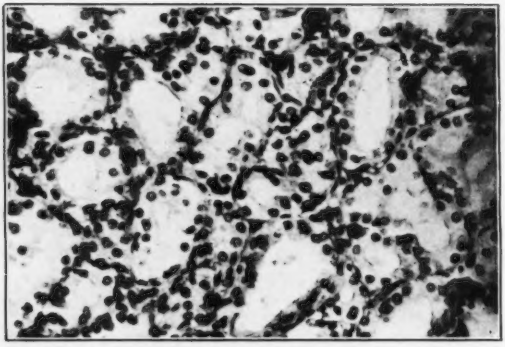

Figure 1. Thyroid gland of white rat after diet consisting of cornmeal, oats and distilled water.

The diet of the third and fourth groups contained the same calcium-rich food, but iodine was added in different amounts. Each animal of the third series was given daily 2 micrograms of potassium iodide, while each rat of the fourth series received 20 micrograms of the same salt. The feeding was continued for a period of 139 days and all animals were killed with chloroform at the end of this period. The thyroid glands were dissected immediately after death, measured and at once preserved in diluted solution of formaldehyde (1:10). Postmortem changes were thus prevented. After embedding in paraffin, the organs were cut in horizontal planes and the sections that included the isthmus and both lobes of the thyroid gland were selected for the microscopic description.

The thyroids of the first group of animals which received only cornmeal and oats, in distilled water, were not entirely normal as had been anticipated. The size of the glands was not increased as compared with control animals, raised in our laboratory on a well-balanced diet. Microscopic study revealed, however,

very slight, but distinct hyperplastic changes. The average size of the acini in the center of the lobes was 40 microns and in the periphery many follicles were much wider. The colloid was, as a rule, well stained with eosin and contained marginal vacuoles. The height of the epithelial lining of the acini was between 6 and 8 microns and the capillaries surrounding the acini were well filled with red blood cells (Fig. 1). Obviously the basal diet had a mild goitrogenic effect. Our findings corroborate the statement by Thompson (13) that the rachitogenic diet of Steenbock produces a slight hyperplasia of the thyroid even without calcium. I do not agree, however, with her view that the low iodine content of this diet was responsible for these changes, because in former experiments I never obtained hyperplasia of the thyroid gland in white rats fed exclusively on pearled barley which was not less poor in iodine than the basal diet used in the present experiment. Apparently cornmeal and oats contain some positive goitrogenic substance the nature of which is unknown. Wegelin also reported large goiters in white rats which received the same diet. However, his experiments were made in a severe goitrous region and we know that domesticated animals in endemic regions will develop thyroid hyperplasia spontaneously. That oats may be goitrogenic, appears likely from the work of Oehme, Paal and Kleine (11), who observed hyperplastic changes in the thyroid of mice when the diet consisted only of oats.

The animals of our group 2 received the basal diet mixed with calcium-rich water. The daily dose of calcium chloride was 0.2 gram for each rat. The effect of this diet was uniform. All white rats showed macroscopically a definite enlargement of the thyroid with marked hyperemia. The size of the centrally located acini was between 30 and 40 microns. Wide acini were exceptional. Many solid and narrow tubular structures were found and the lumina appeared empty or contained scanty, light stained colloid. The acinar epithelium was high (8 to 10 microns) and the hyperemia of the glands was striking. These glands resembled completely those produced in former years by a similar calcium-rich diet and showed again that excess of calcium is a powerful goitrogenic agent. In my opinion, Levine, Remington, Krauss and Monroe, Hayden, Wenner and

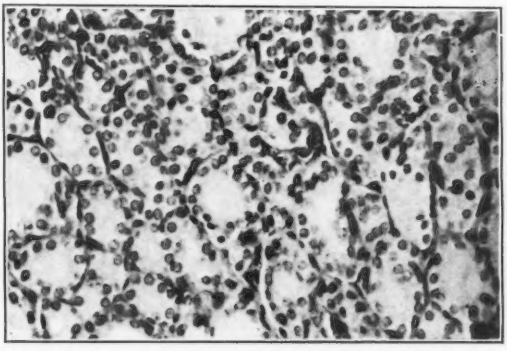

Figure 2. Hyperplastic goiter after diet rich in calcium and poor in iodine.

Rucker were successful in producing goiter in white rats, not because their diet was iodine-poor, as they believed, but because it contained a high amount of calcium. Hibbard, who also observed goiter in rats fed on a diet rich in calcium chloride, believed that the positive element in his series was the chlorine and not the calcium ion, because he found definite hyperplasia in animals fed on a diet high in sodium chloride and none in those fed on a diet high in calcium lactate.

The animals of our group 3 received the same diet as the second, but in addition to calcium-rich water, each animal was given a daily dose of 2 micrograms of potassium iodide. Compared with the physiological optimum recommended by Sollmann for man, this dose represented 10 times the physiological requirements of iodine, per kilogram. In this series, the size of the glands was slightly smaller than in group 2, but was definitely larger than normal. The diameter of the cen-

tral acini varied between 40 and 60 microns; many wide acini were found not only in the periphery but throughout the gland, while solid or narrow acini were almost completely absent. The colloid was well stained with eosin and distended many acini markedly. The height of the acinar epithelium varied between 4 and 6 microns and the blood supply was moderate (Fig. 3). The enlargement

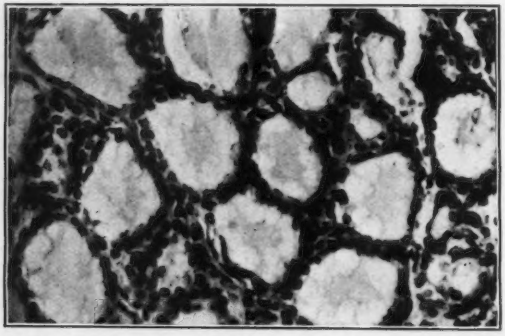

Figure 3. Colloid goiter with slight epithelial proliferation produced by a diet rich in calcium and a daily dose of 2 micrograms of potassium iodide.

of these glands was caused less by hyperplasia of the epithelium than by increased secretion of colloid. The glands of the third series represented small colloid goiters with a very slight epithelial proliferation.

In the last group the white rats received together with a calcium-rich diet a still greater amount of iodine. The daily dose of 20 micrograms of potassium iodide per animal was about 100 times larger than the physiological optimum. The size of these glands was normal. The average diameter of the acini in the center of the lobes was 60 microns and not any solid or narrow tubular acini

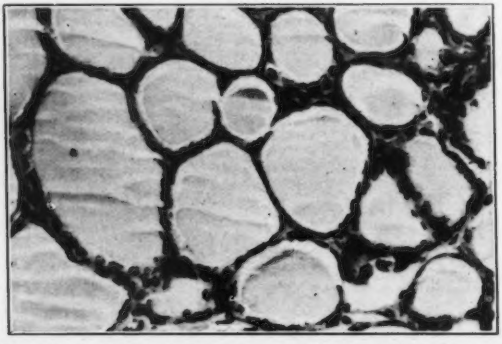

Figure 4. Thyroid of white rat in group 4. Histological structure resembles resting colloid goiter. Diet consisted of cornmeal, oats and calcium chloride. The daily supply of potassium iodide was 20 micrograms.

were found. All acini were completely filled out with dense, deep red colloid which had no vacuoles. The epithelial cells lining the follicles were flattened out. The bood vessels were poorly filled. As far as the size was concerned, these glands were perfectly normal. Microscopically, however, they resembled the resting colloid goiter without epithelial proliferation as seen in human adolescent goiter after effective administration of iodine.

COMMENT

The present experiments have thus shown that goiters can be easily produced in white rats with a diet consisting of cornmeal, oats and calcium chloride. These goiters varied in structure according to the amount of iodine contained in the diet. The enlarged thyroids had small acini and scanty colloid when calcium excess was combined with a low iodine content of the food (Group 2). They were composed of large acini with much colloid when the diet was calcium-rich and iodine-rich (Group 3). In spite of an iodine content 10 times larger than the physiological optimum, the glands of the third group were not entirely without epithelial hyperplasia, since many smaller acini were found.

When the goitrogenic diet was combined with an iodine dose 100 times larger than the physiological optimum (Group 4), the size of the glands was not increased but microscopically the thyroids resembled the resting colloid goiter in man.

The results of these experiments cannot be explained on the basis of the iodine-deficiency theory. In fact, colloid goiter in animals by a diet poor in iodine has never been produced. In order to obtain colloid goiters with epithelial proliferation, 10 times the physiological requirements of iodine was necessary. In the fourth experiment, after receiving 100 times the physiological optimum of iodine, the animals showed thyroids of normal size. While this result supports the well-known prophylactic and therapeutic value of iodine in endemic goiter, it cannot be accepted as proof for the theory that lack of iodine is the essential cause of endemic goiter. Large doses of iodine are, in my opinion, effective in preventing hyperplasia, by stimulating the thyroid secretion and providing a surplus of hormone. The resulting colloid-rich glands produce apparently enough thyroxin to neutralize the effect of the positive goitrogenic factor. My results agree with the view of Loeb and his co-workers (9) that iodine exerts primarily a stimulating effect in hyperplastic thyroid glands. As a result of this stimulation, when an excess of hormone had been produced, Loeb observed enlargement of the follicles and abundance of colloid.

Epidemiological studies have shown that in spite of a very low iodine content of the food, soil and water, a region may be entirely free from goiter (McCarrison) and, on the other hand, in a district with a sufficient amount of iodine, goiter may still be present (Liek). The iodine-deficiency theory is not able to explain these facts. In my opinion, a positive goitrogenic agent is essential for the development of goiter. The effect of the positive factor may be prevented by a very high supply of iodine. In regions where the iodine content of the food is sufficient for a normal intake, goiter will develop if a powerful positive goitrogenic factor is present. Under these conditions, which are found in level regions, the resulting goiter will be colloid-rich. In regions where the food is poor in iodine, as in mountainous areas, the same positive goitrogenic agent will produce

small-follicular, colloid-poor goiters. No goiter, however, will develop, even in iodine-poor soil, if the positive factor is absent.

The results of my experiments are completely in accord with these epidemiological facts.

SUMMARY

The thyroid glands of four groups of male white rats were studied under experimental conditions.

In the first group of seven animals on a diet consisting of yellow corn, oats and distilled water, there was no gross enlargement of the gland, but the microscopic study revealed mild hyperplastic changes.

In the second series of seven animals, the addition of calcium chloride to the same basal diet resulted in a marked increase in the size of the thyroid gland, with pronounced acinar hyperplasia and loss of colloid.

The same calcium-rich diet produced in seven rats a colloid goiter with mild epithelial proliferation when 10 times the physiological requirements of iodine were added.

The thyroid glands of eight animals, fed on a calcium-rich diet with a daily dose of iodine, 100 times larger than the physiological optimum, were of normal size; microscopically, however, they resembled the resting colloid goiter as seen in adolescent human subjects.

Colloid goiter can be produced in white rats by a diet containing a positive goitrogenic agent together with an iodine supply which is higher than the physiological optimum.

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MENSTRUAL RESPONSE TO LUTEINIZING EXTRACT OF PREGNANCY URINE

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Hamblen (1), Novak and Hurd (2) and others describe beneficial changes in menstrual irregularities following the hypodermic injection of a luteinizing extract of pregnancy urine (Antuitrin-S, Parke, Davis & Co.).* Search of the literature revealed no observations on its effect upon normal menstruation. The present brief report deals with this relationship.

MATERIALS AND METHODS

A group of 10 normal women volunteered as subjects for study. Of these, only one was married. Five were medical students and four were studying physical education. Seven were in the third and two were in the fourth decades of life. The married subject was in the fifth decade. The average weight of the ten subjects was 135 pounds and their average height 5 feet 4 inches.

The luteinizing extract of pregnancy urine assayed at approximately 100 rat units per cubic centimeter.

The subjects received 10 injections. The first dose was 1 cc. and subsequent ones 2 cc., if this amount did not create too much local reaction. In that case a smaller dose was given. The injections were given daily, except Sunday. The total dosage varied from 12 to 20 cc., the average being 17.5 cc.

Five individuals received their first doses on the first day of the menstrual flow, and five on a day mid-way between two menses.

Each subject recorded data regarding (a) her menstrual type; (b) the nature of the menses preceding the injection and that of the two succeeding ones with respect to: (1) date of onset of flow; (2) duration; (3) amount in terms of number of pads; (4) presence of clots; (5) presence and amount of pain. The effectiveness of the urine extract in influencing these conditions was taken as the measure of its activity.

RESULTS

First Injection on First Day of Flow. Of the five subjects in this group, four experienced no subjective or objective alteration in the characteristics of their two succeeding menstrual cycles. The fifth individual,

*The authors are indebted to Dr. E. A. Sharp, of Parke, Davis & Co., for supplying the Antuitrin-S used in this study.

eight hours after her first injection, experienced a marked decrease in flow, which returned to normal by the following morning. The duration of this "period" was one day longer than normal.

First Injection Mid-way Between Menses. Of the five persons in this group, one experienced no change in her two subsequent menses.

The second subject felt "prickly pains on both sides of her pelvis, especially on the left." This was first observed after the first menses following injection. It occurred most of the time between this and the following period, and was felt most definitely when turning over in bed. It also was noted after the second menses following injection, but to a lesser degree.

The third subject experienced nothing unusual during or after the first succeeding menses but during the second menses she had a severe dysmenorrhea never experienced previously.

The fourth girl "had pain for 2½ hours—first time in my life—quite surprised—felt as though falling in two" during the first menses following injection. Regarding the next menses she stated "Unconscious of arrival of menses—no heavy feeling in back."

The fifth woman, in the fifth decade of life, experienced her usual three to four days of normal menstrual flow. This was followed by an additional eight days of spotting.* The next period was normal. The one following that also included eight days of additional spotting.

DISCUSSION

The difficulty of enlisting volunteers greatly limited the intended scope of the investigation. Furthermore, the value of any experiment which depends upon an estimation of subjective symptoms is fully realized. These weaknesses were compensated for in part by the intelligence of the subjects.

Injections which were given at the time of the menstrual flow appeared to be without significant influence upon either the feelings of the subject or the characteristics of the flow.

It seems significant, on the other hand, that three of five individuals treated before the onset of the flow experienced entirely new subjective sensations, and that a fourth noted a much prolonged period of "spotting." It is of interest that the latter subject had maintained a record of her menstrual characteristics continuously for a ten-year period. During this time she never experienced any prolongation of her menstrual flow beyond her three to four-day type. On the other hand, two facts suggest that the prolonged period of spotting after treatment may have been due to other factors. The subject was in her fifth decade of life, at the time when the menopause is due, and also the two menses associated with spotting were separated by a "period" of normal length.

*Since going to press it has been learned that the patient injected mid-way between periods, who experienced eight days of unusual spotting, was suffering from a small uterine polyp. Following removal the succeeding menses were normal.

The above observations suggest that the luteinizing hormone of pregnancy urine (Antuitrin-S), given hypodermically before the onset of the menstrual flow, may affect the subjective symptoms associated with the menstrual cycle. That it may also influence the characteristics of the uterine bleeding is not so certain.

SUMMARY

Luteinizing extract of pregnancy urine (Antuitrin-S) injected hypodermically into five normal women, over a ten-day period beginning with the first day of the menstrual flow, was followed by no significant alteration in either subjective symptoms or blood flow during the coexisting or two subsequent menstruations.

Of five women similarly treated, except that the injections were administered beginning with a day mid-way between two menses, three experienced entirely new symptoms of a painful nature, and one other subject had an eight-day period of spotting at the end of a normal three to four-day menstrual flow.

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EFFECTS OF THE INTRODUCTION OF BLOOD FROM BRED RABBITS UPON IMMATURE RABBITS*

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As was first pointed out by Heape (1) and verified by Hammond and Marshall (2) ovulation in the rabbit occurs normally ten to twelve hours following copulation. The work of Evans (3) on the luteinizing effect of anterior lobe extracts upon rat ovaries, and that of Smith and Engle (4) and Zondek and Aschheim (5) on the gonad-stimulating effects of the anterior lobe, as well as that of Smith (6) showing that hypophysectomy caused cessation of the oestrus cycle in the rat all indicated a relationship existing between the anterior lobe and the ovary. Bellerby (7) working with hypophyseal extracts and Friedman (8) working with pregnancy urine were able to induce ovulation in the unbred rabbit and Fee and Parkes (9) have demonstrated that hypophysectomy within one hour following copulation prevents ovulation. This, in broad outline, is the evidence for the belief now commonly held, that ovulation in the rabbit is the end product of two reactions: first, an activation of the anterior lobe probably by means of the nervous system, resulting from the stimulus of copulation, and secondly, activation of the ovary as a result of the production of anterior lobe hormone.

The exact mechanism of the first phase is not known. Evans and Long (10) have shown that artificial insemination is not effective; Fee and Parkes (11) found that vaginal anesthesia by means of novocaine and percaine does not affect the occurrence of ovulation although Meyer, Hisaw and Leonard (12) report that the percentage of rats becoming pseudo-pregnant was greatly reduced if stimulation of the cervix occurred under general anesthesia.

As regards the second phase, i.e., actual ovulation presumably as a result of an increased output of anterior lobe hormone, there is a great deal of confirmatory evidence. No attempt will be made here to review the abundant literature on this point. It is undoubtedly true that follicular changes can be induced in the ovary of the immature rabbit by the introduction of anterior lobe preparations and that ovulation does not occur in the absence of the hypophysis. However, to be conclusive, it should be possible to demonstrate that there is an increased amount of anterior lobe hormone circulating in the blood following copulation as compared to the amount found at other times.

Parkes and Brambell (13) have recently attacked this phase of the problem from the standpoint that if the concentration of anterior lobe

*This investigation was aided by a grant from the National Research Council, Committee on Research in Problems of Sex.

hormone in the blood rises following copulation then removal of part of the blood and its replacement by gum acacia solution should lower the concentration and prevent ovulation. They believe that the number of follicles maturing bears some relation to the concentration of hormone in the blood and extirpation of some follicles will result in the maturation of others on a lower hormone concentration. Jares (14) is in agreement with this belief. He finds that a certain minimal concentration is necessary for rupture to occur; beyond this point and, within certain limits, the number of follicles rupturing is in proportion to the amount of pregnancy urine injected.

In the present investigation we have attacked the problem from the point of view that if a sufficient amount of blood from a bred rabbit could be introduced into immature, unbred females, ovulation should occur. Cross-circulation experiments were attempted but clotting difficulties, as well as the consideration that only about a fifty per cent concentration could be expected, rendered such attempts unfeasible. A technic whereby it was possible to obtain a hormone concentration in the immature animal approaching that of the bred donor was then developed and some positive results obtained. About 150 rabbits, pure bred white New Zealand does, were used, the donors being fully matured and the recipients varying from 12 to 18 weeks of age.

EXPERIMENTAL

Three series of experiments were performed with certain variations in technic. In the first series, a preliminary study was made to ascertain roughly what amounts of blood would be necessary and the time following copulation at which the hormone concentration was at its maximum. The donors were bled to death from the carotid artery, the blood permitted to clot and the serum introduced either intraperitoneally or intravenously. Table I shows the results.

TABLE I

Number Rabbits Used	Post-Copulatory Time	Amount Injected Into Each Recipient	Site of Injection	Time Killed, Post-Injection	Results
2	12 hours	20, 40 cc.	Intra perit.	24 hours	Negative
2	10 hours	25, 35 cc.	Intra perit.	24 hours	Negative
2	8 hours	40, 60 cc.	Intra perit.	24 hours	Negative
2	4 hours	40, 50 cc.	Intra perit.	36 hours	Negative
4	2 hours	20 cc.	Intravenous	36 hours	Negative
6	1¾ hours	30 cc. (Div. Dos.)	Intravenous	36 hours	Negative
3	1½ hours	40 cc. (Div. Dos.)	Intravenous	36 hours	Negative
3	1½ hours	60 cc. (Div. Dos.)	Intravenous	36 hours	1 positive

This study indicated that large amounts of blood would be necessary and that the peak of hormone concentration was probably reached rather early following copulation. In the second series the donors were again bled to death and the blood defibrinated as rapidly as shed. The recipient was anesthetized and from 40 to 60 cc. of blood was removed from the

carotid. From 60 to 100 cc. of the defibrinated donor blood was then slowly injected into the jugular vein, the carotid tied off and the animal returned to its cage. Forty-eight hours later it was killed and the ovaries examined. Six male donors and six unbred female donors, used as controls and treated in the same manner, gave negative results. The results of this series are shown in Table II.

TABLE II

Rabbit Number	Post-Copulatory Time	Amount of Blood Removed From Recipient	Amount of Blood Introduced From Donor	Time Killed Post-Injection	Results
B- 1	1½ hours	45 cc.	60 cc.	54 hours	Negative
B- 2	1¾ hours	50 cc.	95 cc.	51 hours	Positive
B- 3	1¾ hours	55 cc.	100 cc.	51 hours	Positive
B- 4	1½ hours	60 cc.	95 cc.	52 hours	Positive
B- 5	1¾ hours	65 cc.	65 cc.	52 hours	Negative
B- 6	1½ hours	40 cc.	100 cc.	51 hours	Negative
B- 7	1½ hours	45 cc.	100 cc.	30 hours	Negative
B- 8	1¾ hours	45 cc.	75 cc.	48 hours	Positive
B- 9	1½ hours	50 cc.	100 cc.	48 hours	Negative
B-10	1¾ hours	50 cc.	100 cc.	48 hours	Positive
B-11	1½ hours	45 cc.	95 cc.	48 hours	Negative
B-12	1½ hours	45 cc.	100 cc.	54 hours	Negative

Since only five of twelve animals responded positively in the preceding experiment it seemed that the hormone concentration in the recipient animals was still not high enough. In the third series the following technic was employed. Three mature rabbits were bred for each recipient, bled to death and the blood defibrinated. The recipient was anesthetized and the ovaries examined to make sure they were immature. At four-minute intervals the animal was alternately bled and injected with bred blood in 40 cc. amounts until a total of from 200 to 350 cc. of bred blood had been introduced. Results are shown in Table III. Six control experiments using males and six using unbred females, treated in the manner described, gave negative results.

TABLE III

Rabbit Number	Post-Copulatory Time	Amount of Blood Removed From Recipient	Amount of Blood Introduced From Donors	Time Killed, Post-Injection	Results
C- 1	1¾ hours	200 cc.	220 cc.	51 hours	Positive
C- 2	1½ hours	212 cc.	260 cc.	50 hours	Negative
C- 3	1½ hours	200 cc.	220 cc.	56 hours	Negative
C- 4	1½ hours	200 cc.	260 cc.	50 hours	Negative
C- 5	1 hour	250 cc.	260 cc.	65 hours	Positive
C- 6	1 hour	290 cc.	300 cc.	51 hours	Positive
C- 7	1 hour	260 cc.	280 cc.	64 hours	Positive
C- 8	1 hour	270 cc.	300 cc.	64 hours	Negative
C- 9	1½ hours	300 cc.	350 cc.	60 hours	Negative
C-10	1½ hours	250 cc.	300 cc.	65 hours	Negative
C-11	1 hour	280 cc.	300 cc.	49 hours	Negative
C-12	1 hour	235 cc.	250 cc.	48 hours	Positive
C-13	1 hour	230 cc.	240 cc.	65 hours	Positive
C-14	1 hour	280 cc.	300 cc.	64 hours	Positive
C-15	1 hour	240 cc.	260 cc.	64 hours	Positive
C-16	1 hour	240 cc.	260 cc.	60 hours	Positive
C-17	1 hour	260 cc.	300 cc.	64 hours	Positive
C-18	1 hour	270 cc.	290 cc.	65 hours	Positive

The last six experiments in this series, all of which resulted positively, were performed in March and April, while the preceding twelve were carried out during the winter months.

Plates showing representative positive responses appear below.

DISCUSSION

There appear to be two points requiring discussion. First, the failure of many animals to respond positively, although treated in exactly the same manner as the others. This, we believe, is due to too low a concentration of hormone. Probably the amount produced is not greatly above the minimum required to produce ovulation in any case; if, as indicated by the work of Parkes and Brambell previously cited, the number of follicles maturing is in proportion to the concentration of hormone, then,

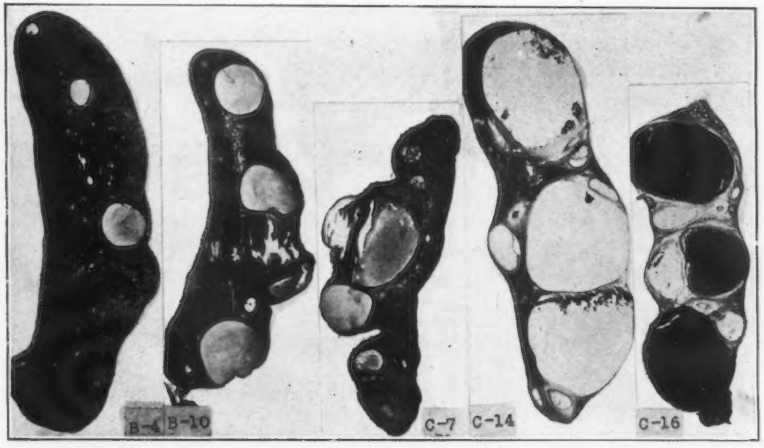

Figure 1. Cross sections of rabbit ovaries showing representative positive responses. See Tables II and III.

conceivably, the amount of hormone present limits the size of the litter and one would not expect it to be present in excessive amounts. Also, one might reasonably expect that there would be a difference in the amount produced in different individuals and possibly individual differences in the sensitivity of the ovaries of the recipients. The concentration of hormone in the circulation of the recipient was rarely greater than 85 per cent that of the donors and this, in the negative cases, may have been too low to produce a response.

The second point is the nature of the response. In only one case, animal B-4, were true corpora lutea found. In all other cases the response was essentially that of a positive Zondek-Aschheim reaction. Corpora hemorrhagica, in some cases with the ovum enclosed, predominated. The formation of corpora hemorrhagica might conceivably be due to the in-

creased blood pressure causing a rupture of capillaries into the follicles, but the fact that the animals giving negative results as well as the controls had increased blood volumes in many cases to an even greater extent argues against such a view. It would seem that this question involves the more general problem concerning the exact nature of the so-called precocious sexual maturity in the female, a problem which, we believe, still demands a great deal of experimental study.

SUMMARY

This paper describes experiments which attempt to demonstrate a higher concentration of anterior lobe hormone in the blood of bred rabbits than in unbred animals by its action upon the ovaries of immature animals.

1. Immature females injected with 60 to 100 cc. of blood from bred rabbits killed between one and two hours following copulation responded positively in five of twelve cases.

2. Immature females alternately bled and injected with blood from bred rabbits at four-minute intervals until 200 to 350 cc. had been introduced, responded positively in eleven of eighteen cases.

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QUANTITATIVE HORMONE REQUIREMENTS*

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DETROIT

The frequently repeated request concerning the amount of hormone required in the treatment of endocrine disorders has stimulated thoughtful consideration of this topic. So far, however, no general rule has been established beyond the assertion that an attempt should be made to meet the individual requirements. As opposed to hormones, the older and better known drugs are frequently assumed to have an established dosage, so that the average graduate from medical school has quite a definite idea of the kind and amount of drug to be employed when a definite disease or condition has been diagnosed. By comparison they expect similarly definite statements concerning hormone requirements. Careful reflection, however, will show that even the standard drugs exhibit considerable variations in their actions. A few of these drugs credited with a specific action and dosage will be mentioned here for comparison with the hormones.

The evolution of digitalis therapy is somewhat analogous to the hormone dosage problem. Although even in medieval times the leaves of digitalis, when chewed, were known to have a definite effect, it was not until the year 1785 that the derivatives of this plant received general attention. At that time Withering wrote: "Let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects"—a dictum which is still sound. Since Withering's time many refinements in the use of the drug have been developed; namely, standardization by pharmacological experiments with better preservation of the products, with more accurate check as to their deterioration, sharper definition of the indications and contraindications for its use, and elucidation of its manner of action in the pathological states for which it is employed. Intelligent use of digitalis now requires knowledge of the pharmacological action of the drug, including recognition of evidences of intoxication, as well as the potency of the product employed, determination of the indications and contraindications for its use, and appreciation of the individual patient's requirements for complete digitalization. It is evident that those most skilled in the use of digitalis individualize, considering many factors, and are not bound by textbook statements concerning dosage.

Arsphenamine, or similar products, are of more recent origin than digitalis. They are often stated to have a definite dose for specific indications. Many syphilologists start with six-tenths gram of neoarsphenamine,

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as a routine initial dose, following which practically all patients experience some slight anorexia. Varying with the individuals, this may be followed by nausea and even vomiting, sometimes extreme, protracted vomiting. The variation in reaction often seems to be due to the nervous stability or instability of the individual to whom the injection is given. However, other systemic factors may be present; for instance, severe damage has been proved in some occasions to follow the administration of the average dose. Another type of sensitivity to neoarsphenamine is the appearance of an exfoliative dermatitis following the administration of amounts stated as suitable dosage or even less. Reactions vary not only with the amount of the drug given and the frequency of injections, but also with individual susceptibility. This drug is another illustration of variation in reaction to standard dosage.

Belladonna, and its derivative atropin, have long been accepted as standard drugs. The limit of tolerance of these drugs seems to have a wide variation. Recently one individual, an average sized adult, experienced dryness of mouth with anything more than two drops of tincture of belladonna, in spite of the fact that the dose is stated to be five to fifteen minims. A few years ago a patient received one grain of atropin sulphate by subcutaneous injection, following which she exhibited serious symptoms of atropin poisoning, but made a complete and satisfactory recovery. Another patient experienced delirium following administration of one seventy-fifth of a grain of atropin sulphate, though the dose is stated to be one one-hundred-twentieth to one-sixtieth grain. These three instances illustrate the variation in susceptibility to the belladonna group.

Pilocarpin, a physiological antagonist of atropin, may be cited as another drug to which individual susceptibility is variable. Medicinal doses, one-twelfth to one-half grain, may produce no obvious effect, while similar doses have been known to cause serious and even fatal results.

The sedative group represents a different type of reaction, inasmuch as the psychic state of the patient is of even more importance in this group than with other drugs. Sodium amytal, so popular in the past few years, in the majority of instances is sedative to some extent; in some instances, however, the opposite effect is induced, the drug becoming a delirifacient. Psychiatrists tell us that the effect of this drug depends much upon the personality background as well as possible endocrinological factors. One or two illustrations of the exception to the general sedative reaction may be mentioned: first, a psychoneurotic individual with hysterical mechanisms showed no sedative reaction from double the average dose of sodium amytal, but, on the contrary, on the day after operation she was so stimulated that she got out of bed and started wandering about the room. A second patient, who had been operated upon for repair of the perineum and cystocele, became confused as to the relation of a retention catheter, pulled it out, got out of bed, and walked about the room. While neither of these patients was psychotic, they should be considered as psycho-

neurotic—a condition which must be carefully evaluated, especially in the use of sedative drugs.

Anesthetic drugs are seldom prescribed in definite quantities. One would hesitate to say that for a particular operation or for a stated duration of anesthesia a dosage of three ounces of ether, or a fixed number of gallons of nitrous oxide, would be indicated. Satisfactory use of the anesthetic drugs depends upon the anesthetist following the patient carefully during the administration of the anesthetic, and varying the amount of the drug according to the symptoms manifested by the patient as the indicator. All the mixing chambers for estimating percentages of anesthetic mixtures are merely an aid to the anesthetist in controlling the amount of the drug administered. Regardless of statements as to percentages and quantities needed, every skilled anesthetist depends entirely upon the symptoms manifested by the patient for final judgment as to the dosage needed.

So it is quite evident that therapeutic agents other than hormones have a wide variation in the indications for the use, in the amount to be administered, in the indications and contraindications for the individual drug, in the average manner of action and the quantitative results produced by a fixed dosage. Furthermore, the reactions of the individual patient to any therapeutic agent should be the criteria for the final determination of the manner and amount to be administered. No doubt many of the unsatisfactory therapeutic results with a wide variety of drugs depend upon lack of careful attention to the indications and individual susceptibility.

Years have been consumed in arriving at an established dosage of standard drugs which can be stated in the pharmacopeia, therefore when one deals with a problem of such recent origin, as the hormones, it is not to be expected that a fixed dosage could have been established in so short a time. Just as with other therapeutic agents, it is important to consider a large number of variables before deciding upon the proper amount of the remedy to be administered. Any drug is given for a specific action, though some drugs may be valuable for more than one purpose. The same is true of hormones. Some may be said to have a specific action and to be indicated within very narrow limits, while others have very wide indications for their use. It seems advisable to try to review some of the important factors which must be considered in arriving at a proper dosage of hormones.

In a consideration of specific hormone therapy, thyroid takes precedence on account of its wider use. The most commonly used preparation of thyroid is the extract of the whole gland which undoubtedly owes much of its popularity to the fact that it may be administered successfully by mouth, as well as to the readily recognizable indications for its use. Like other hormones, thyroid extract does not stimulate the gland from which it is derived, but merely supplies a deficiency; therefore the obvious indication for its use is hypothyroidism, and conversely the contraindication is

hyperthyroidism. In spite of its long use, the exact manner of action of thyroid extract is not well known. To establish the level of function of the thyroid in an individual by the basal metabolic rate, which too often is considered diagnostic, is not accurate, for the rate may not be truly basal. Furthermore, other conditions, e.g., undernutrition, and pituitary disturbances, may give a low basal rate and unappreciated psychic stimulation may elevate the supposed basal rate.

Assuming that a correct diagnosis of hypothyroidism has been established, can the required amount of thyroid necessary to overcome the deficiency be accurately predicted for the individual? The answer must be negative for, at present, there is no accurate measure of the deficiency of the gland, and standardization of the drug is not based upon any biological test. The outstanding requirements of the U. S. Pharmacopeia are not less than seventeen-hundredths and not more than twenty-three hundredths per cent of iodine in thyroid combination. Does this method of standardization really indicate the active principle of the gland extract?

It is quite possible that the product may vary considerably in potency when taken from animals collected from different regions, having individual cyclic variations. Further complication in estimating the dosage of thyroid is added by the cyclic variation of the individual to be treated. All of these variants necessitate employment of criteria similar to those used for anesthesia; namely, the reactions of the individual treated. Failure to individualize may result disastrously.

The following illustrative case reports are given only in brief, inasmuch as a large portion of each record abstracted has no bearing on the point to be illustrated, and to include the unrelated details would be confusing; therefore, only such portions are submitted as are directly related to the application of hormone.

Case 1. T. B., age 22, was treated for irregularity of menstruation and sterility. The history was unimportant except that which related directly to the condition of irregularity of menstruation and sterility.

MENSTRUAL RECORD

	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933
January	16	..	..	20	8	..	17	22	..	9
February	22	4	1 & 18	..	9	2	18	22	6	18
March	27	4	31	..	24	10	..	..	9	21
April	..	6	..	..	27	8	27	13	24	Pregnancy
May	..	11	2	2	31	15	..	26	..	
June	30	..	10	16	..	16	13	18	3	
July	..	25	21	21	13	25	..	11	20	
August	..	22	..	24	30	..	7	14	..	
September	2	5	..	..	..	1	11	25	..	
October	..	11	1	12	..	3	13	..	1	
November	..	30	9	..	8	20	17	4	20	
December	..	..	21	13	9	..	..	..	..	

Although there was disturbance of rhythm, the amount of flow was above average (four days heavy flow, and three days scant). She gave a history of having had a goitre at the age of twelve, which disappeared with treatment; the nature of this treatment she did not know. The first six years of her life

she lived near the Gulf of Mexico; the last sixteen years she lived in Detroit. The patient was of average stature, five feet, four and three-quarters inches in height and weighed 119 pounds. There was slight thinning of the eyebrows, brittle nails, the patient tired easily, the blood pressure was 90/58, pulse 80, and her estimated basal metabolic rate was minus eleven per cent. Pelvic examination showed that the uterus and ovaries were well developed and in good position. There was a masculine distribution of hair on the pubis. The mechanical findings in the pelvis were essentially negative.

There had been a history of sterility for three years, together with the disturbed rhythm of menstruation. Treatment was started on November 21, 1932. She was given one-half grain of thyroid twice daily for two weeks. On December 5th the dose of thyroid was increased to three half grains a day, and on December 19th to two grains a day. The patient seemed to improve on this latter dosage, and this level was maintained throughout. She did not menstruate in December, but did menstruate on January 9, 1933, February 18, 1933, and March 21, 1933. When seen in May, 1933, she was pregnant, the apparent duration of the pregnancy corresponding to the last menstrual date of March 21st. The February and March menstruations were more nearly normal in amount. During the time she was observed the blood pressure varied from 100/58 to 120/80. This case illustrates a prompt reaction to an amount of thyroid that might be predicted as necessary in consideration of the patient's metabolic rate and physical findings.

Case 2. E. T. E., age 23, was seen March 23, 1931, for irregularity of menstruation. She began to menstruate at the age of 15; menstruations were never regular, for there were intervals of three or four months. Duration of the flow was five days, with an average amount, as a rule. For the past year there had been occasional pain on the first day of menstruation, and some headaches. At the age of 12 to 13 the patient grew very rapidly in height, and when first seen by us was six feet one and one-half inches tall. At the age of 17 to 18 she began to take on weight, gaining to 160 pounds. She had an appendectomy for a ruptured appendix at the age of 7, and was in bed for three months. The patient has taken active outdoor exercises. Examination showed a palpable thyroid; pulse 88; blood pressure 130/80; there was slight dryness of the skin; and the uterus was small but within normal limits. The basal metabolic rate was plus one per cent. In spite of the slight suggestion of hyperthyroidism, thyroid therapy was cautiously tried, beginning with one-quarter grain of thyroid twice a day. At the end of a month the thyroid extract seemed to be well tolerated. The blood pressure then was 110/70. The weight remained the same. On April 24, 1931, she began to menstruate, the previous period having been in January. She menstruated again June 14, 1931. On June 29, 1931, the blood pressure was 96/74, and weight 157 pounds. Thyroid was increased to one and one-half grains a day, and on July 31, 1931, theelin was started, giving fifty units a day, intranasally, for a period of three months at intervals of two weeks. The patient administered this drug herself. She tried taking two grains of thyroid a day, but began to show a few symptoms of overactivity of the thyroid. She was instructed about the symptoms to be expected from too much thyroid, and was taught to regulate the dose herself, as she lived at a considerable distance and was unable to come to the office regularly. She found that her tolerance varied from time to time, and that she could tolerate from one and one-half to three and one-half grains a day. At the end of eighteen months she reported that she was menstruating regularly, and felt in excellent physical condition. Her blood pressure, originally at 130/80, varied in the systolic chiefly, going as low as 100, and the diastolic as low as 70.

This case is of interest in that the thyroid was not only tolerated in spite of a plus one per cent basal metabolic rate, but apparently was necessary and served as an important factor in the patient's improvement of menstrual irregularity. Furthermore, this very intelligent patient was able to regulate her own dose of thyroid, and thereby demonstrated the variation in amounts needed at different times. Whether this variation was due to the difference in the products, or to the variation in the patient's condition is a question not easy to answer.

Case 3. M. H., aged 23, was seen in October, 1930, because of irregularity of menstruation, which had been present since onset. She expressed great fear that this irregularity was a serious menace to the condition of her general health. She did not complain of fatigability, drowsiness, or lack of eneregy; in fact, she stated that she was well except for this irregularity of menstruation. The basal metabolic rate determination at that time was minus fourteen per cent, height sixty-seven and one-half inches, weight 132 pounds, pulse 78, and blood pressure

110/70. She was given one-half grain of thyroid a day. On December 22, 1930, her blood pressure remained the same (110/70), and her weight was 130 pounds. The thyroid was increased to two grains a day, and the patient was instructed about signs of overactivity of the thyroid. On May 11, 1931, her weight was 129½ pounds, and blood pressure 100/60. The menstrual flowing occurred about every twenty-five days. In the meantime the patient had been visiting in Arizona. In June, 1931, she went to Europe, and stayed there for three months. Having been informed of the symptoms of thyroid overactivity she continued to take thyroid extract during this trip, but did not menstruate all summer. When seen on September 28, 1931, her blood pressure was 110/80, and weight was 119 pounds. She had been taking about three grains of thyroid a day the few weeks preceding this visit. The patient was last seen June 8, 1932, at which time her blood pressure was 102/70, weight 122½ pounds, and pulse 76. She felt in excellent general condition, and had been menstruating regularly for several months, and flowed an average amount each time. She had learned her tolerance of thyroid, and found that two grains was insufficient, but anything over three grains gave her signs of overactivity. This case illustrates hypothyroidism predicted by basal metabolic rate findings and irregular menstruation, also the effect of change in environment on the condition of hypothyroidism. Furthermore, the patient was intelligently cooperative, and was able to determine her own level of thyroid therapy, and on such a regime maintained a normal menstruation.

Case 4. R. G., age 29, was seen February 5, 1930, because of frequent miscarriages. The patient was unwilling to undergo any investigation at that time, and miscarried at four and one-half months, on April 26, 1931. She was advised that we found evidence of hypothyroidism, as there was very dry skin, thinning of the eyebrows, tendency to gain weight, drowsiness, easy fatigability, cold extremities, brittle hair and nails, and the repeated miscarriages. The basal metabolic rate, however, on May 29, 1931, was recorded as normal average. On June 4, 1931, thyroid treatment was begun with a dosage of one-quarter grain, three times a day. On June 15, 1931, it was increased to one-half grain twice a day. On August 3, 1931, there was some improvement in the dryness of the skin, and there was less fatigability. Her last period was August 9, 1931, after which she became pregnant. She continued taking one and one-half grains of thyroid a day throughout the pregnancy, went to full term, and delivered a normal baby on May 19, 1932. Fellowing delivery, the thyroid therapy was continued, and opportunity then presented to determine her tolerance. She required from three to four grains a day, and under the administration of this amount most of the previous symptoms of hypothyroidism disappeared. This case illustrates another instance in which the hypothyroidism could not be predicted from the basal metabolic rate. The patient was a highly nervous individual, and it was probably impossible to get basal conditions. The physical findings, the history, and the response to therapy are the best proofs of the hypothyroidism in this instance. The case also illustrates the important relation of hypothyroidism to miscarriages.

Follicular hormone may be assayed biologically, but the rat unit varies according to whether the minimal amount necessary to produce full oestrus in a castrated rat is determined by one or more injections. Chemical standardization is possible through purification and crystallization. Although fairly accurate standardization of the hormone is possible, the deficiency for which it is to be used is difficult to measure. Therefore, indications for the amount to be used must depend upon the results obtained.

The crucial test for the efficiency of ovarian follicular hormone necessitates demonstration of activity of this product in the absence of ovaries. While many cases may be cited to show that a deficiency has been supplied when ovaries are present, there is no means of measuring this deficiency accurately, other than a response to therapy. The cases reported by Werner and Collier (1) illustrate the reaction of the uterus to theelin in that they have not only produced growth of the uterus, but a definite

bleeding. In our earlier work (2) one of the striking symptoms reported was detection of growth of the uterus following the administration of even small doses of follicular hormone. It cannot be stated, as yet, that the amounts needed in the individual cases can be well predicted.

Another hormone, pitocin, a fraction of the posterior lobe of the pituitary, stimulates contraction of smooth muscle. It may be assayed biologically, but the indications for its use must be weighed carefully. The amount needed varies with the individual, and from time to time in the same individual. Failure to regard these variations has caused many an obstetrician to class it as a dangerous agent. But careful determination of the amount needed obviates all danger and safeguards its use. This is another example of the amount and method of application being controlled by the reaction of the patient.

Case 5. M. W., age 43, the mother of two children, gave a history of fairly regular menstruations, but in June, 1929, she had continuous flow for three weeks. She was given pitocin with a nasal spray, and at the end of four days the flow stopped, becoming less each day. She was advised to repeat the procedure if the bleeding was prolonged the following month. She flowed again the 18th to 27th of July, and then began the pitocin, and within three days the flow stopped. After that the periods were relatively normal. The exact cause of the bleeding was not determined in this instance, but it illustrates one use of pitocin in cases in which there is excessive flowing without any grossly demonstrable anatomical lesion. It apparently may be used frequently without any harmful results. In such cases it seems to be more effective if given in frequently repeated doses. An intelligent patient is able to determine the amount needed by the results obtained.

Case 6. M. M., age 33, was seen on account of execessive flowing, which was due to endometriosis of the uterus and ovaries. The patient was very desirous not to have both ovaries removed, and also was determined to retain her uterus, although she knew that the bleeding might not be stopped by partial resection of the ovary. On January 16, 1928, the left tube and ovary, and a part of the right ovary were removed on account of the endometriosis. There was still some of the endometrial growth in the wall of the uterus. The uterus should have been removed at this time, but only in consideration of her expressed desire was it left in situ. The postoperative convalescence was uneventful, the patient leaving the hospital on the seventeenth day. After returning home, she remained well until time for the next menstruation, when she flowed excessively, so that it was necessary to bring her back to the hospital on account of the anemia. Transfusions were given. At that time intranasal pituitrin was used, which proved very beneficial in stopping the flow. The patient was informed of the nature of the pituitrin and its action, so that she could regulate the amount of pituitrin necessary according to the amount of flow. By this means she was able to carry on for four years. It was necessary for her to use the intranasal pituritrin with every menstruation. Pitocin was tried, but was not so effectual as pitruitrin. The endometriosis in the uterine wall extended, and pain became an added feature, so that hysterectomy was necessary. This case emphasizes the possibility of a patient administering pituitrin to herself to overcome excessive flowing. Also, there was great variation in the amount needed from time to time to overcome the flowing which made it essential that the patient should be under direct control.

Case 7. C. W., age 24, was first examined October 14, 1932. Her first pregnancy began August 2, 1932. At the time of examination the blood pressure was 138/100. It remained approximately at that level until March, 1933, when it increased to 150/114. The patient was admitted to the hospital, and the diet and fluids regulated; but in spite of that the blood pressure continued to rise a little, reaching at its highest 200/130. Following rest in bed the diastolic remained constant, but the systolic dropped slightly for about two weeks. Then, in spite of the careful hospital regulations, both the systolic and diastolic pressures began to ascend. It seemed necessary to induce labor. Castor oil and quinine were given with little effect. Pitocin was given intranasally to test the

patient's limit of tolerance, and then hypodermically in doses of two to four minims, according to the patient's reaction. In order to keep the patient well rested the pitocin was interrupted from time to time, and a sedative given. On April 17, 1933, eight injections of pitocin were given, and on April 18th, eight additional injections were given. This was sufficient to start active labor, although it was three weeks ahead of the predicted date. A normal child was born.

The particular reason for citing this case is to illustrate the possibility of relying upon pitocin for induction of labor even in the presence of high blood pressure. The blood pressure was not raised directly by the injection of the pitocin, but did show some increase when the patient was having continuous hard labor pains and not receiving pitocin. The number of injections apparently is of very little consequence, so long as the individual dose is kept below the patient's limit of tolerance. As many as forty injections of pitocin have been given to one individual without evidence of harmful effect.

Anterior-lobe-like substance, prepared from urine of pregnant women, can be assayed biologically according to the amount necessary to produce luteinization of follicles, and therefore its potency may be expressed in rat units. It has been used successfully in the treatment of some metrorrhagias, but the amount required varies considerably in different individuals and at different times in the same individuals.

Case 8. J. K., age 38, complained of prolonged, excessive menstrual flow for the past seven months. In November, 1928, the regular period continued with uninterrupted flow until the time for the December period, which was excessive. The January, 1929, period was accompanied by three weeks' flow with many hemorrhages, which were lessened by keeping off her feet. She had a curettage in March, 1929, which showed polypoid endometrium. Then followed essentially normal menstruations for two years. The period in May, 1931, was normal, but later in the month spotting appeared and continued until the period in June. Excessive flow followed the June period. The patient's hemoglobin was 81 per cent, and red blood count 4,450,000. On June 30, 1931, a curettage was done. The uterus was in retroposition, a large average, but of uniform consistency. There was no evidence of fibroids. The ovaries appeared to be normal on palpation. The pathological report showed hypertrophy of the endometrium. She did not menstruate following the curettage until October 14, 1931, when she began to flow excessively. In February, 1932, the patient flowed excessively, but was relieved promptly with antuitrin-s (injection of 50 rat units each on six consecutive days). Then she was normal for the next several months, but the latter part of November, 1932, she bled profusely. She was given some of the hormone which had been kept by a local physician for a year, and it was without effect. On pelvic examination there was no particular change from the previous findings. The uterus was a little large and soft, but nothing abnormal noted in the adnexae. The excessive flowing was again relieved by the injection of antuitrin-s, 50 rat units, on six consecutive days. This case is typical of many already reported in the literature (Novak, 3). This form of therapy is particularly effective in cases in the later years of the reproductive cycle.

Case 9. M. C., age 14. Not all cases of hypertrophy of the endometrium respond favorably to anterior-lobe-like substance. The following case illustrates an unsatisfactory result. This girl had been followed for a number of months by her local physicsian who had tried various drugs, including thyroid, to stop the bleeding. The bleeding was excessive from the onset of menstruation, and had kept the child out of school for a considerable part of the time for the past two years. There seemed to be some difference of opinion as to what should be done for the child's condition; one physician having recommended removal of the ovaries, and another continuation of the conservative treatment. A compromise was finally made and a laparotomy was performed, at which time the appendix was removed and the pelvic organs were inspected. Both ovaries at that time showed numerous follicle cysts, larger than the average, but no corpus luteum. A curettage. showed microscopically, typical hypertrophy of the endometrium with the dilated glands. Following curettage there was no flowing for two months, then the flowing became almost continuous, and in large amount. Antuitrin-s was given, but unfortunately in each of two instances it was given just

at the onset of the flow. It seemed to exaggerate the flow, until on the second occasion, after three daily injections of antruitrin-s, one hundred rat units each, the patient bled so profusely that she became unconscious and three transfusions were necessary before she recovered. The parents refused to have this therapy repeated, and I have been informed that a hysterectomy was finally performed.

Another illustration of anterior-lobe-like substance used at an early age, at which hyperthrophy of the endometrium occurs, is shown in the following:

Case 10. M. J. M., age 13½, was first seen June 15, 1932. Menstruation began at the age of 13, the first period having started December 23, 1931, and was of five days' duration. The second period was January 24 to 28, 1932. There was no further menstruation until March 6 to 10, 1932, and again April 3 to 9, 1932. Each of these periods became a little more profuse. In May she flowed continuously from 1 to 15. She started again on May 29, 1932, and continued to June 13, 1932. She was given injections of 100 rat units of antruitin-s each day from June 15 to 21, 1932, inclusive. The following period occurred June 26 to July 4; the next August 2 to 6, and 24 to 29. Following this there was a period of amenorrhoea until January, 1933. Since then she has been flowing regularly, an average amount, and duration of about five days. The diagnosis of hypertrophy of the endometrium could only be assumed from the character of the flowing simulating other cases of similar nature. She gave evidence of hypothyroidism. The blood pressure was as low as 86/50; pulse 60-80. She complained of dry skin and brittle nails. Unfortunately she could not be induced to get a basal metabolic determination, but on the basis of symptoms she was given a prescription for one-half grain of thyroid twice a day. This was begun in January, after her period of amenorrhoea. In February this was increased to one and one-half grains, and when last seen in June, 1933, she had been menstruating regularly and flowed a normal amount. The symptoms were striking, but the diagnosis remained presumptive, but whatever the diagnosis, the patient has been relieved of her symptoms.

Other hormones could be analyzed in a manner similar to the four already cited. But these suffice to emphasize the importance of individualization in every instance. Endocrinology is still a new subject and the method of trial and error will need to be employed for a long time before standardization can be approximated. Many changes of opinion will necessarily occur.

From the foregoing statements it will be seen that the administration of hormones is controlled in a manner quite similar to that of standard drugs. Chemical and biological assays serve only as a guide to the potency of the therapeutic agent. After careful consideration of the indications for use, the criteria for determining the amount required should be, in all cases, the reaction of the individual patient.

Animal experimentation is far ahead of clinical application in the field of endocrinology. Species variation prevents the direct application of laboratory results to clinical problems. Extravagant claims could be eliminated if the clinician instituted accurate controls similar to those employed in the experimental field.

SUMMARY

The average medical student leaves school with the impression that, given a diagnosis, there is a fixed standard dosage of therapeutic agents to be administered. This is shown to be erroneous even in such old standard drugs as digitalis, arsphenamine, belladonna and its derivatives, pilocarpin, sedatives, e.g., sodium amytal and anesthetics. Therapeutic agents, including hormones, have a wide variation in the indications for use, the amount

to be administered, the indications and contraindications, the manner of action, and the quantitative results produced. In a consideration of hormone therapy, thyroid takes precedence on account of its wider use. Four brief case reports are given illustrating the use of thyroid extract. Three of the subjects were treated on account of menstrual irregularity, and one for repeated miscarriages. Only two of them had a low basal metabolic rate from which thyroid insufficiency could be predicted. One showed considerable variation from time to time in amount of thyroid tolerated. Follicular hormone is cited for its growth effect on the uterus, and the work of Werner and Collier noted on account of theelin producing bleeding from uteri of castrated women. Three cases are reported in which posterior pituitary lobe products were used, two of which were for stopping excessive flow, and one for inducing labor in a woman who had essential hypertension. Three other case reports include the use of anterior-lobe-like substance for controlling bleeding from hypertrophy of endometrium: two successfully; one unsuccessfully. One subject was approaching the menopause. The other two were girls at the age of thirteen. The criteria for the amount of any therapeutic agent to be used should be the reaction of the individual patient.

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ENDOCRINE STATISTICS FROM THE SOUTHEAST*

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The incidence of endocrine disorders in various parts of the North and West is fairly well known, and several statistical analyses have appeared in the literature. Less is known of the relative frequency of the appearance of several endocrinopathies in the Southeast, and the present data have been compiled to correct this omission. This record derives from the files of the Good Samaritan Clinic in Atlanta, Ga., a city which is geographically the center of the area under consideration. While a majority of the patients are residents of the city or county, a fair proportion come from other portions of the state or from those states adjoining it. The present figures, on this basis, may be regarded as fairly representative, particularly as the Clinic is the only one in the entire section devoted exclusively to endocrine disorders. A free clinic, maintained by public funds and aided by some individual private gifts, it enjoys no hospital facilities and thus can receive only ambulatory cases. When a diagnosis has been established, the patient is referred to that member of the staff in whose special field the patient properly falls, and whose free treatment determines the continuance of the contact. The clinic is staffed by a group of 26 physicians representing 14 of the special fields of medicine; it is housed in its own building, which provides clinic space, laboratories, an x-ray department and the other necessary physical equipment including the record office.

Extensive laboratory and radiographic studies are carried out on each patient during the period of diagnostic study and, in general, all focal infections are eradicated before opotherapy is initiated. As is inevitable in any endocrine clinic, a very significant percentage, 27 per cent in this series, of the cases referred on the basis of symptoms or other stigmata suggesting an endocrine disorder are found to have conditions unrelated to the ductless glands. Such patients are referred to the other clinics maintained in the city.

The present statistical analysis is derived from the study of 1363 consecutive cases, studied in the Clinic during the past ten years. The 363 were patients with non-glandular disorders and drop out of further consideration. Of the 1000 cases finally diagnosed as of endocrine causation on which this analysis rests, the general distribution is given in Table I.

The thyroid cases constitute almost exactly one-half of the entire series, while the remainder are almost equally divided between the two major

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TABLE I
COMPOSITION GROUP

Condition	Male	Female	Total
Thyroid Disorders	133	366	499
Pituitary Disorders	106	162	268
Gonad Disorders	39	178	217
Miscellaneous Endocrine Disorders	7	9	16
	285	715	1000

remaining endocrinopathies associated respectively with the pituitary and the gonads. Adrenal cases here as elsewhere are but rarely encountered, and our list shows a vanishingly small number of cases of diabetes. The ease and certainty with which this latter condition can usually be recognized undoubtedly explains the small number resorting to our Clinic. About one in four were males, figures that agree well with the sex distribution deriving from other sources.

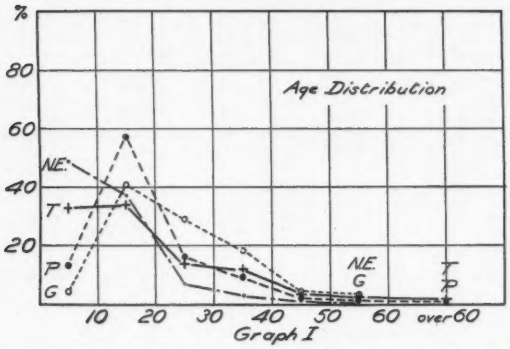
Although Atlanta, in common with all southern cities, has a large colored population—almost exactly one-third—the members of this race form a very small part of the group under consideration. Of 55 colored patients examined, there were but 48 with established endocrine disorder, grouped as follows:

TABLE II
ANALYSIS OF COLORED PATIENTS

Condition	Male	Female	Total
Thyroid Disorders	4	19	23
Pituitary Disorders	4	9	13
Gonad Disorders	0	11	11
Pancreas Disorders	1	0	1
	9	39	48
No Endocrine Disorder	3	4	7
Totals	12	43	55

Both the etiological and sex distribution in this group parallel very closely that in the larger series from which they are drawn. The unexpectedly small number of colored patients may be explained possibly by the fact that people of this race do not regard disability as serious unless accompanied by pain or distress. It is also possible that there are actually fewer cases of endocrine disorder among the colored race. Not improbably both of these factors play a part. In 1931 the colored division of the Atlanta city hospital reported but three endocrine diagnoses. The Georgia State Board of Health reports that about 25 per cent of all blood Wassermanns sent in are found to be positive. In view of the general belief, the small number of luetic cases, about 2 per cent, may also be surprising, but there are records in the Clinic on several adult colored virgins. The large number of females and the large proportion of hypo-functional conditions are characteristic in both white and colored races.

The age scatter can best be presented graphically.



Percentage scatter in decades of the patients in the several major groups.

Over 50 per cent of the pituitary cases come between the ages of 11 and 20 years; the thyroid group shows 67 per cent between birth and 20 years, while the gonad disorders appear most commonly between the ages of 11 and 30 years, and continue in high numbers up to 50 years. With the female dominance in this group, the age scatter here is what normally might be anticipated. The non-endocrine group, included here solely for the sake of completeness, appeared chiefly in the early years, and the incidence was highest before 10 years of age; this results from the fact that the chief sources of these cases are the public schools and Juvenile Court.

Fewer thyroid patients admitted previous tonsillitis and fewer had surgical removal of the tonsils prior to admittance. This may account for the possible effect on the thyroid of chronically infected tonsils, a relationship already noted in the literature. A large percentage of all thyroid patients without previous operation were found to have infected tonsils and adenoids. Previous operative interference in ear, nose and throat conditions was less in the thyroid group, while gastro-intestinal and pelvic operations were four to six times higher in the gonad group. This observation is in harmony with similar reports already published elsewhere.

A history of previous thyroid operation was practically confined to those patients showing current thyroid disorders. Only one such operation was reported in the entire pituitary group. In all other reports of previous surgical operation, the gonad series again leads.

For the sake of brevity, the significant record of previous disease is collected in tabular form. For purposes of completeness, the like records of the non-endocrine group are included.

The other major disease catagories were so rarely reported as to make inclusion here unnecessary. A detailed analysis of the incidence of acute infections in contrast to their appearance in 40,000 unselected cases recently analyzed by the Committee on the Cost of Medical Care is somewhat interesting.

TABLE III

PREVIOUS ILLNESSES

Reported in Percentage

Condition	Pituitary	Thyroid	Gonad	Total Endocrine	Non-Endocrine
Acute Exanthemata	69	70	49	63	66
Cardio-Respiratory	31	28	28	29	18
Head and Throat	39	34	41	38	22
Metabolic Disorders	9	7	1	5	5

The apparent discrepancy between the percentage of acute exanthemata in Table III and the percentage of the diseases in Table III-a is explained by the fact that pertussis, mumps and diphtheria are not classed as acute exanthematous diseases but are placed in the cardio-respiratory and head and throat groups.

TABLE III-a

ACUTE INFECTIONS

Condition	Present Series (1000)	Committee Report (40,000)
Measles	88	89
Mumps	58	63
Pertussis	57	77
Chicken Pox	45	52
Diphtheria	7	10
Scarlet Fever	7	11

Where significant difference exists, it is in favor of the endocrine group. The explanation for this somewhat unexpected finding is not immediately forthcoming. Certainly endocrine disorders do not confer immunity to acute infections, and our findings here are the opposite of those recorded from other sources.

Reverting to Table II, there seems to be an increase in cardio-respiratory and head and throat conditions in the endocrine group; the remaining series show good agreement. Reference to the detail reports from which the summary was compiled shows the following. A high incidence of epistaxis among thyroid cases is notable. The gonad series showed a considerably higher incidence of measles, mumps, malaria, influenza, tonsillitis and rheumatism than do the other groups. Epilepsy was common in the gonad series, and not reported in the other endocrinopathies. This again is contrary to usual experience where a pituitary association has been frequently noted. Asthma was similarly classified. A low incidence of scarlet fever among ovarian patients was unusual and unexpected; chorea was more prevalent in pituitary patients, as was also nephritis and colitis.

With practically all of this series of 1000 patients resolved into three major endocrine categories, the distribution of the several function levels in each warrants careful scrutiny. As the thyroid group was the largest, it may be considered first.

TABLE IV

DISTRIBUTION OF THYROID CASES

Condition	Male	Female	Total
Hyperthyroidism—			
Thyrotoxicosis	10	61	71
Thyroid adenoma	1	23	24
Exophthalmic goiter	3	24	27
Adolescent goiter	2	37	39
Thyroiditis	0	1	1
	16	146	162
Hypothyroidism—			
Thyroid failure	110	142	252
Cretins	6	9	15
	116	151	267
Non-toxic Dysplasias—			
Non-toxic adenoma	0	48	48
Cystic adenoma	0	1	1
Colloid goiter	1	20	21
	1	69	70
Grand Total	133	366	499

Thyroid failure patients outnumber those showing hyperactivity almost two to one, as might well be expected; the sex distribution in the former group is more nearly at a parity than in any other. There were 15 cretins, six of whom were male. Exophthalmic goiter in the male is rare, but the series contains three such patients, and what is even more unusual, one of them was colored. Thyroiditis is reported but once; it seems probable that mild cases of this condition are escaping notice. One case of calcipexy, or calcium stiffening of the muscles, was encountered. The incidence of lues was about 1 per cent, which is similar to the reported incidence elsewhere. The only suspected etiologic factor, aside from heredity, which from the data might seem to have a bearing in many of these cases, was influenza. It is interesting to note that the reports of premature and twin births appeared almost solely in the thyroid group. Reports of overterm gestation appeared uniformly among the different disorders classified. The average age of the total thyroid series was 18.6 yrs.; the average birth weight, 7.89 lbs.

In the next table the pituitary data are assembled.

TABLE V

DISTRIBUTION OF PITUITARY CASES

Condition	Lobe		Male	Female	Total
	Anterior	Posterior			
Hyperfunction	+	+	29	23	52
Imbalance	−	+	37	27	64
Imbalance	+	−	29	111	140
Hypofunction	−	−	10	2	12

One-fifth of the series showed hyperfunction, the group evidencing a slight male preponderance. The imbalance group practically absorbs the remainder; the partition between the two types here is unusual as the common report of pituitary dysfunction presents the type in which the anterior lobe is underactive while the posterior lobe is overactive. Bilobar failure is but sparsely represented: as this is frequently the terminal phase of an earlier imbalance or even hyperfunction, the youth of the group may account for its low incidence in this series. There were but five possibly positive Wassermanns and but two of these gave four plus readings.

As all of the gonad patients presented functional failure, detailed tabulation is unnecessary. From Table I it may be recalled that the females were 178 in number as opposed to 29 males. The average age of this group was 24 years. Only two positive Wassermanns were found, and one of these had been positive before clinic entrance, but was negative at time of admission. As was noted previously, the gonad group had a dominantly high record of laparotomy. Concretely, the percentages are: pituitary, 7.9; thyroid, 7.8, and gonad 25.2. A report of two or more abdominal operations was also considerably higher in the gonad group, the incidence being four times as frequent as in the thyroid series and over 25 times as among pituitary patients.

Among other possible etiologic factors, head trauma (including birth injuries) was reported in 15 pituitary, 24 thyroid and 14 gonad patients. The scatter of other injuries offers an uninformative distribution; the operative factor has already been touched upon.

There is one other datum contained in the Clinic records that may be suitably considered here. This is the moot question of breast vs. bottle feeding and the possible influence of the early nutrition on the subsequent level of function and health. The pertinent data are condensed in the next table. Again, the non-endocrine group is included as a control.

TABLE VI

POSSIBLE INFLUENCE OF BREAST FEEDING

Datum	Thyroid	Pituitary	Gonad	Non-Endocrine
Birth Weight (average)	3.8 kg.	3.6 kg.	3.3 kg.	3.3 kg.
Breast Fed	74.2%	86.4%	81.4%	76.5%
Bottle Fed	25.8%	13.6%	18.6%	23.4%
Diseases Reported in—				
(a) Breast Fed	4.2%	4.6%	5.6%	3.2%
(b) Bottle Fed	4.5%	4.6%	7.0%	3.2%

With the possible exception of the gonad series, there is no significant difference in the frequency of reported diseases in the two major divisions; with the gonad group, the limited length of the series urges caution in any far-reaching interpretation of the apparent difference. Broadly speaking, breast feeding seems to confer no marked advantage at least in regard to the subsequent incidence of disease.

SUMMARY

Statistics are cited from 1363 consecutive active cases from the Good Samaritan Clinic of which 1000 have been classed as endocrine; in other words, one in four presumptive endocrine cases showed a non-glandular condition simulating an endocrinopathy. The diagnosis was based upon the gland predominatingly affected, and thus no pluri-glandular conditions were classified, as such. This is for simplification of classification, and does not deny the importance of recognizing interrelated functions. Hypofunctional levels predominated in all groups; the thyroid patients composed half of the total number of endocrine patients, while the pituitary and gonad sections constituted the greater part of the remainder. Many of the figures are in harmony with reports from other parts of the country. Twin and premature births were recorded chiefly in the thyroid group. In age comparison, the thyroid group first appeared in largest measure before adolescence, while the pituitary group was at its height at this period. The gonad group maintained a fairly uniform level from maturity to 50 years. Head trauma was reported more frequently in the pituitary and gonad groups. The thyroid patients had fewer tonsillectomies prior to clinic entrance, but a larger incidence of infected tonsils on examination. The average birth weight was in the thyroid than in the pituitary and gonad groups. The gonad patients had undergone previous laparotomies far more frequently than had the thyroid and pituitary patients. The very low incidence of colored patients may be due to the racial disregard for non-disabling conditions, to an actual lessened susceptibility to endocrinopathy, or to both of these factors.

In conclusion, the author wishes to express his deep appreciation of the friendly services of his associates of the Good Samaritan Clinic from the concerted efforts of whom these clinical studies have come into being.

THE EFFECTS OF VARIOUS COMPOUNDS OF THYROXINE ON THE BASAL METABOLISM*†

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Many different compounds of thyroxine may be prepared which may have different effects on the basal metabolism. It would be impossible in the time allowed for this paper to discuss in detail even the observations that we have made on the effects of a few compounds. For the purpose of simplicity we shall confine our attention largely to a comparison of the effects of administering thyroxine intravenously in alkaline solution with those of administering thyroxine in various forms by mouth.

A Comparison of the Effects of Prolonged Oral Administration of Pure Thyroxine, Monosodium Thyroxine and Desiccated Thyroid with the Effects of Administering Thyroxine Intravenously. In one patient with myxedema we have observed a definite response to the prolonged oral administration of large doses of pure thyroxine suspended in distilled water. The thyroxine was given in daily doses of from 7.5 to 50 mgm. over a period of eight months. Final figures are not yet available, but it would seem that the basal metabolism, which was about minus 40 per cent before treatment may be held at the normal level by the daily administration of approximately 50 mgm. of pure thyroxine. In four other patients (1) whose basal metabolisms were minus 33 per cent, minus 41 per cent, minus 34 per cent and minus 25 per cent during the myxedematous state, the rates were minus 19 per cent, minus 12 per cent, minus 24 per cent and minus 10 per cent during the daily oral administration of 1 mgm., 2 mgm., 1 mgm., and 1 mgm., respectively, of pure thyroxine. This substance was given after the basal metabolism had been raised to normal by other compounds. The observations in these four patients covered periods of only about two months, which may have been inadequate to determine exactly the effects of the doses administered.

In six patients with myxedema and a basal metabolism of minus 30 per cent on the average, it was necessary to administer an average daily dose of 1.1 mgm. of monosodium thyroxine by mouth in order to hold the

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basal metabolism at the normal level (1). In two of these patients, with an average basal metabolism of minus 37 per cent during the myxedematous state, the normal level was maintained by an average intravenous dose of 0.33 mgm. of thyroxine containing 0.21 mgm. of iodine. In the same two patients an average of 1.33 mgm. of monosodium thyroxine had to be administered by mouth daily in order to accomplish the same result. In brief, the effect was one-quarter as great as that of thyroxine administered intravenously but much greater than the effect of pure thyroxine by mouth. In the same two patients the metabolic rate was also held at the normal level on the average by the daily administration of 1.38 grains of desiccated thyroid‡ containing 0.21 mgm. iodine. Thus, the maintenance doses of thyroxine given intravenously in an alkaline solution and of desiccated thyroid given by mouth were the same on the basis of total iodine contents.

A Comparison of the Effects of Oral Administration of Single Large Doses of Pure Thyroxine, Monosodium Thyroxine, Thyroxine in Alkaline Solution and Desiccated Thyroid, with the Effects of Intravenous Injection of Single Large Doses of Thyroxine in Alkaline Solution. All data on this point which have been previously published (2) (3) or are in press (1) (4) (5) have been summarized in Table 1. For purposes of comparison, all changes have been arbitrarily reduced to terms of 10 mgm. of thyroxine or its equivalent in total iodine content. The interesting thing is that pure thyroxine in doses as large as 100 mgm. by mouth does not have a demonstrable effect on the basal metabolism, while the effect of oral administration of the monosodium salt is 22 per cent as great as the effect of injecting thyroxine intravenously in alkaline solution, the effect of oral administration of an alkaline solution is 63 per cent as great and the effect of oral administration of desiccated thyroid is 69 per cent as great.

According to Kendall, when thyroxine is dissolved in an excess of sodium hydroxide the disodium salt is formed. Pure thyroxine is very insoluble, while the monosodium salt is slightly soluble and the disodium salt soluble to the extent of 4 per cent [Kendall (6)]. The solubility of the thyroxine compound administered would, therefore, appear to be a very important factor in its absorption from the gastro-intestinal tract and hence in its effect on the basal metabolism. It is of interest that desiccated thyroid has, on the average, about the same effect as thyroxine in alkaline solution when the two are administered by mouth in single large doses containing the same total amounts of iodine. According to Harington and Salter (7), thyroxine exists in the gland as a constituent amino-acid of iodothyreoglobulin. These observers separated a polypeptide of thyroxine from the gland which they said had a wide range of solubility and which Salter, Lerman and Means (8) showed had nearly as great an effect on metabolism when given orally as when given intravenously. Following three oral administrations of this substance they noted an average increase in basal

‡The desiccated thyroid referred to was kindly supplied to us by Dr. Klein of the Wilson Laboratories.

TABLE 1

A COMPARISON OF THE EFFECTS OF ORAL ADMINISTRATION OF SINGLE LARGE DOSES OF PURE THYROXINE, MONOSODIUM THYROXINE, THYROXINE IN ALKALINE SOLUTION AND DESICCATED THYROID WITH THE EFFECTS OF INTRAVENOUS INJECTION OF SINGLE LARGE DOSES OF THYROXINE IN ALKALINE SOLUTION

Medication	Iodine Content of Substance Administered Mgm.	Number of Patients	Number of Administrations	Average B.M.R. Before Treatment, Per Cent. Normal	Average Level to Which B.M.R. Rose, Per Cent. Normal	Average Change in B.M.R. Points	Average Change in B.M.R. in Terms of Response to Intravenous Injection, Per Cent.[7]
10 mgm. of thyroxine intravenously in alkaline solution[1]...	6.5	6	8	−37	− 5	32	100
10 mgm. of pure thyroxine by mouth suspended in distilled water[2].....	6.5	4	4	−32	−30	2	6
10 mgm. of pure thyroxine by duodenum suspended in distilled water[3].....	6.5	3	3	−30	−29	1	3
10 mgm. of thyroxine by mouth in the form of the monosodium salt[4] (tablets).....	6.5	6	6	−28	−21	7	22
10 mgm. of thyroxine by mouth in alkaline solution[5].....	6.5	5	5	−31	−11	20	63
2.83 gm. of desiccated thyroid by mouth in tablet form[6]...	6.5	5	5	−37	−15	22	69

1. All doses were 10 mgm. except two which were 7.5 mgm. The effects of these two were reduced to terms of 10 mgm. by multiplying the number of points change in basal metabolism by the fraction 10/7.5. All thyroxine referred to in this paper was the synthetic thyroxine of Hoffmann-La Roche, except that Squibb's crystalline thyroxine was used for four of the intravenous injections.

2. The actual doses administered were 10, 30, 40 and 100 mgm.

3. The actual doses administered were 10, 40 and 50 mgm.

4. The actual doses administered were 7.5, 10, 10, 10, 30 and 40 mgm. The changes in basal metabolism were reduced to terms of 10 mgm. as indicated in the first footnote of this table. The greatest change noted was one from minus 37 per cent to minus 25 per cent following the oral administration of 10 mgm. All of the monosodium salt referred to in this paper was administered in the form of Hoffmann-La Roche tablets, each of which contained 1.03 mgm. of the salt.

5. All doses were 10 mgm. except one of 7.5 mgm. which was corrected for as indicated in Footnote 1. The alkali used was always sodium hydroxide.

6. All doses were 2.75 gm. except one of 2.05 gm. Their effects were changed to terms of 2.83 gm. by a method similar to that recorded in footnote 1.

7. In calculating this figure, the number of points change in the basal metabolism was divided by 32 and the result multiplied by 100.

metabolism, reduced to terms of 6.5 mgm. of iodine (the amount contained in 10 mgm. of thyroxine) of from minus 36 per cent to minus 6 per cent; that is, a change of 30 points as compared with our changes of 20 and 22 points, respectively, for the oral administration of thyroxine in alkaline solution and desiccated thyroid. The reason for this difference in effect is not clear at present. Dr. S. Nadler of New Orleans has recently prepared thyroxine peptide with an iodine content of 48 per cent by proteolytic digestion of the gland according to the method of Harington and Salter. We have found this substance to be insoluble in water but to be soluble in alkali and to give, when administered in a suspension of distilled water by mouth, less than half as much effect as thyroxine in alka-

line solution by mouth. Its effect in an alkaline solution was at least as great as that of thyroxine administered in the same form (9).

Since the duodenal contents are alkaline, it seemed to us desirable to observe the effect of administering thyroxine directly into the duodenum. Accordingly we gave 40 mgm. through a duodenal tube to one patient with myxedema and 50 mgm. to another. In neither case was there a demonstrable effect on the basal metabolism. In other words, it would seem that the alkalinity of the small intestine is not great enough to cause the solution of more than a very small fraction of the thyroxine.

Our data suggest that the oral administration of a given amount of desiccated thyroid may produce a greater effect if it is given in small doses every day over a long period than if given in a single large dose. The reason for this difference is not certain. When a single large dose is administered by mouth some may be destroyed in the gastro-intestinal tract or simply fail to be absorbed.

SUMMARY

In terms of the amount which had to be administered every day in order to hold the basal metabolism of patients with myxedema (basal metabolism minus 37 per cent) at the normal level, it appeared that thyroxine when given intravenously in alkaline solution (0.33 mgm. daily) had about four times as much effect as when given by mouth in the form of its monosodium salt (1.33 mgm. daily) and about 150 times as much effect as when given by mouth suspended in distilled water (50.0 mgm. daily), while thyroxine given intravenously in alkaline solution and desiccated thyroid given by mouth (1.38 gr. daily containing 0.21 mgm. of iodine) appeared to have the same effect on the basis of equivalent iodine contents.

Single doses of from 10 to 100 mgm. of pure thyroxine administered by mouth and single doses of from 40 to 50 mgm. administered directly into the duodenum produced too small an effect on the basal metabolism to measure with accuracy.

In patients with myxedema a single intravenous injection of 10 mgm. of thyroxine in alkaline solution caused the metabolism to increase 32 points (from minus 37 per cent to minus 5 per cent on the average), while the oral administration of equivalent doses of monosodium thyroxine, thyroxine in alkaline solution and desiccated thyroid caused changes in the metabolism 22 per cent, 63 per cent and 69 per cent, respectively, as great.

Thus, when the effects of single large doses are compared, 10 mgm. of thyroxine when given by mouth in an alkaline solution, has the same effect as a dose of desiccated thyroid containing the same amount of iodine (6.5 mgm.).

The effect of thyroxine when administered by mouth seems to depend upon the solubility of the compound administered.

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TREATMENT OF PITUITARY INFANTILISM WITH ANTUITRIN

REPORT OF CASE

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Engelbach (1), particularly, has called attention to the syndrome of infantilism based on pituitary hypofunction and with Schaefer and Brosius (2) has reported a series of cases treated with growth hormone from the anterior lobe. Falta (3) reports the stimulation of growth with Praehormon in two cases of infantilism.

The rarity of treated cases in the literature is the inspiration for the presentation of this case, particularly, also, as this patient was treated with Antuitrin as such, rather than with a growth fraction of the anterior lobe hormone such as was available to Engelbach and his co-workers.

CASE REPORT

W. L., age 17 years and one month, was given the routine examination for entrance into the Municipal Boys' Home, New Orleans, January 9, 1933.

Family History. The father died of tuberculosis in 1917 and the mother died of the same disease in 1928. One brother is living and well, and one sister is living but is crippled as a result of "spinal meningitis."

Past History. The boy had had the usual childhood diseases but detailed developmental history of the first decade is absent as the patient had lived in the homes of relatives and in orphanages. The patient states that his mother was small, but that his brother was of normal size.

On August 31, 1927, the patient had been examined in the Pediatric Clinic of Touro Infirmary. The tonsils were found to be enlarged and diseased. The tuberculin test was weakly positive. The urine contained albumin and granular casts. On September 19, 1927, and October 27, 1927, the urine was normal. The tonsils were removed on October 29, 1927.

He was suspected of having tuberculosis and was sent to Greenwell Springs Sanatorium on September 17, 1931. He remained there until April 14, 1932, when he was dismissed as an arrested case. It is questionable whether pulmonary tuberculosis ever existed. At the time of entrance the Sanatorium had no x-ray machine and when the patient left there was no evidence of lung disease.

Examination (January 9, 1933). The patient did not complain of any symptoms but the examiner was struck with the small stature of the patient. He had known that he was small but had paid little attention to it. He could not state definitely whether growth had stopped suddenly at any age, or whether the slowness of growth had been chronic throughout life. The patient had no sex desire and had known ability to erect and ejaculate only in the previous two months. He had never shaved.

The measurements on this date are shown in Table 1. There was a slight down on his upper lip, a few axillary hairs, and moderate pubic growth of hair confined to the suprapubic region. The penis in the relaxed condition measured two and seven-eighths inches in length, considered a small normal.

The temperature was 98.6 and the pulse 64. Examination of the head, neck, chest, abdomen, and extremities gave normal findings. The urine and feces were normal. The Wassermann test gave negative findings. The complete blood test findings and basal metabolism were within normal limits.

X-ray examination of the hand, wrist, foot and ankle on January 11, 1933, showed that the epiphyses were not united. In addition, the radiologist stated, "The impression is gained, however, that the proximal phalanges of the hand and foot are longer than commonly observed, and appear out of proportion to the bones in this vicinity."

Treatment was begun on January 18, 1933, with an arbitrary dose of 1 cc. of antuitrin (Parke-Davis) every other day.

Course. Treatment was continued until April 28, 1933, at which time the patient had grown in height from 60.5 inches to 62.12 inches. Treatment was discontinued from April 28, 1933, until June 5, 1933, during which time no growth occurred. On June 5, 1933, treatment was commenced and continued until August 2, 1933. (See Table 1.) The patient then left the city to go to school and passed out of immediate observation.

TABLE I

	Normal Variations (Engelbach)	Jan. 9, 1933	April 28, 1933	July 5, 1933	Aug. 2, 1933
Height	63.2– 67.6	60.5	62.12	62.12	62.37
Weight	103. –131.	98.			101.
Span	65.0– 70.	61.			62.5
Upper Height	30.7– 33.7	29.5	Treatment	Treatment	30.12
Lower Height	31.8– 34.8	31.	Stopped	recommenced	32.25
Circumference of head	22.2	21.			21.
Circumference of chest	32.9	28.5			28.5
Circumference of waist	27.8	27.			25.

On January 18, 1933, x-ray examination of the left elbow showed open epiphyses, and a second examination on April 10, 1933, showed no change in the epiphseal unions.

On July 31, 1933, the radiologist's report states: "At this examination the epiphyses at the lower end of the humerus are not yet united with the shaft, nor is the radial head or olecranon process united with its respective shaft. In comparison with the previous radiographs a slight growth may be considered to have occurred in the various epiphyses about the elbow, but the changes are very minor."

A total of sixty-seven injections of Antuitrin were given. After the first month of the treatment, the authorities of the Home noticed, and the patient admitted, a great increase in the libido, as evidenced by frequent masturbation. In addition, whereas prior to the treatment the boy was inclined to be shy and retiring, during treatment the patient became the radical of the Home, the first to go to the Superintendent to complain of real or fancied wrongs.

After the third month of treatment, hair growth on the upper lip was marked and the patient began to shave.

SUMMARY

The case of a boy of 17 exhibiting the cardinal features of pituitary infantilism is reported. Coincident with a course of 67 injections of Antuitrin (Parke-Davis) the patient gained approximately two inches in height and showed objective evidence of increased sex drive as well as personal aggressiveness. During a ten-weeks' interval when treatment was omitted no growth occurred.

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AN ATTEMPT TO DUPLICATE CERTAIN HORMONE RESPONSES BY MEANS OF DRUGS

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In the response to the gonad-stimulating hormone in pregnancy urine, as well as in that to estrin, there is a tremendous increase in the blood supply to the genital organs. It has frequently been suggested that the so-called "Blutpunkte" might be due entirely to this hyperemia. It seemed possible, therefore, that the increased blood supply might be the cause of the stimulation of ovaries and testes and of the development of the secondary sex organs and that drugs which produce such a hyperemia might also bring about similar changes in the genital organs.

As drugs which would produce hyperemia of the genital organs, yohimbine and cantharidin are well known. In addition, histamine, by causing dilation of the vessels, might increase the blood supply to this region appreciably.

Yohimbine, cantharidin, and histamine, in dosages as large as could be tolerated, were administered to 21-day-old rats over a period of 10 days. The animals were sacrificed and ovaries and seminal vesicles were carefully dissected and weighed. Uninjected rats of the same age were used as negative controls. Pregnancy urine was injected for three days into 21-day-old rats and the animals sacrificed 100 hours after the first injection. These served as positive controls. As seen in the table, there was no increase in weight of seminal vesicles or ovaries following the drugs. A noticeable hyperemia of the genital organs was produced by yohimbine and cantharidin, but this was not comparable to that which followed injection of pregnancy urine. In no case was there opening of the vagina or increase in the size of the uterus, nor were there any hemorrhagic follicles, changes which were observed following the use of pregnancy urine.

The experiment with yohimbine and cantharidin was repeated on young female rabbits. Three rabbits were given 10 mg. per kilo of yohimbine per day for four days and the abdomens opened. There was noticeable hyperemia, but no ripe follicles. One rabbit, given 2 mg. per kilo per day of cantharidin, died after 48 hours. Another given 1 mg. per kilo the first day and ½ mg. per kilo the second, died on the third day. In both there was very marked hyperemia, but no ripe follicles.

Ludwig and von Ries (1) recently reported that yohimbine in doses of 1/20 to 1/10 mg. and cantharidin in doses of 5/1000 to 10/1000 of a mg. will produce estrus in immature mice. Presumably only one dose was injected. They conclude that the production of estrus is not specific for

WEIGHTS OF SEMINAL VESICLES AND OVARIES

Treatment	Dosage Per Day	Males	Average Weight	Seminal Vesicles	Females	Average Weight	Ovaries
Control		13	50.5 gm.	9.1 mg.	15	46.5 gm.	17.7 mg.
Histamine	10. mg.	6	48. gm.	7.5 mg.	7	44.7 gm.	16.1 mg.
Cantharidine	.03 mg.	5	48. gm.	10.5 mg.	6	44.6 gm.	16.6 mg.
Yohimbine	.4 mg.	6	52. gm.	8.5 mg.	6	49. gm.	16.0 mg.
Pregnancy urine	1. cc.	7	32. gm.	46.9 mg.	6	32.6 gm.	34.5 mg.

estrin. To test their results, 10 ovariectomized rats were injected each day for seven days with 0.25 mg. cantharidin and 10 with 4 mg. of yohimbine. The vaginae were smeared twice each day. No estrus smear appeared.

SUMMARY

The action of drugs which induce a hyperemia of the genital organs was studied in an attempt to determine whether the responses to the gonad-stimulating hormone of pregnancy urine and to estrin might be due to the hyperemia which they produce.

Yohimbine, cantharidin and histamine were injected into groups of 6 male and 6 female 21-day-old rats daily for a period of 10 days. Noticeable hyperemia was produced, but no increase in size of uteri, opening of vaginae or hemorrhagic follicles. There was no increase in weights of seminal vesicles and ovaries over those of uninjected controls.

Yohimbine and cantharidin given respectively to three and two young female rabbits for four and two days produced marked hyperemia, but no ripe follicles.

No estrus smears were obtained when groups of 10 ovariectomized rats were injected with cantharidin and yohimbine each day for seven days.

The degree of hyperemia which is produced by dosages which can be tolerated is not comparable to that which follows injection of the hormones. The question as to whether the hyperemia following hormone injection is the underlying cause for the development of the gonads is unsettled.

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NERVOUS AND HORMONAL FACTORS IN LACTATION

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Our knowledge of the factors controlling lactation has greatly advanced in recent years. It is now clear that we must distinguish sharply between the formative stimuli which cause full development of the mammary gland, and the functional stimuli which cause the developed gland to enter into active secretion. The studies of Stricker and Grueter (1) and especially of Corner (2) on the rabbit may offer some difficulties in interpretation, but there is abundant evidence that in the rat, mouse, and guinea-pig the hormones of the ovary act as formative stimuli; the relative importance of oestrin and the corpus luteum hormone is a matter of controversy, and possibly varies from species to species. The work of Turner (3), Riddle (4), Nelson (5) and many others indicates that the anterior hypophysis contains a hormone (prolactin, galactin) capable of acting as a functional stimulus, and experiments on hypophysectomized cats (6), rats (7), and mice (8) prove that this factor is essential for the continuance of lactation. Many problems, however, still await decision, among which are important questions of correlation. What stimuli, it may be asked, induce the anterior hypophysis to secrete prolactin? In what manner is this secretion regulated, so that lactation ceases and mammary involution occurs when the young are removed? By what mechanism is oestrus prevented in lactating rats and mice with litters of normal size? In this paper we report the results of experiments which offer clues to the solution of these three problems.

It has been urged that an abrupt decrease in the concentration of circulating ovarian hormones, such as probably occurs at about the time of parturition, may act as a stimulus to the hypophysis to produce prolactin. This view is supported by the observation that lactation may occur at the end of a period of administration of ovarian hormones (9, 10), and by our own finding (11) that removal of the intensely luteinized ovaries from virgin rats treated with the anterior-pituitary-like substance leads to milk secretion, provided that the hypophysis is intact. There may also be cited in favor of this view the fact that established lactation can be inhibited by the administration of oestrin in the rabbit (12) and mouse (13), and in the latter species also by administration of the ovary-stimulating anterior-pituitary-like hormone (14). We ourselves have recently seen rapid and complete inhibition of established lactation in rats receiving this hormone in conjunction with a hypophyseal extract containing thyreotropic and gonad-stimulating factors. We injected six normally lactating rats with 50 units of A.P.L. and 1 cc. of the pig pituitary extract on the third and fourth days

of lactation and we found that on the evening of the second day of treatment the stomachs of the young were empty. The litters received no nourishment from thenceforward and eventually died. Histologically, the mammary glands of these rats still showed signs of milk secretion but their activity seemed to be considerably decreased. It is highly probable that the inhibiting influence of ovarian hormones upon lactation is exerted by way of the hypophysis rather than by direct action on the mammary glands, though this question can hardly be settled until means are found to maintain lactation in hypophysectomized animals. Our own experiments in this direction have not been successful. We have not been able to maintain lactation in hypophysectomized rats by means of pituitary implants. In a series of eight lactating rats, we implanted each animal with 1-3 rat pituitaries daily for three days; the rats were then hypophysectomized, the treatment with implants being continued. These rats stopped lactating just as quickly as the untreated animals in our previous experiments.

There are, however, certain other facets of this main problem. We (15) have found in the rat, as others have found in various species, that removal of the foetuses by Caesarian section before term leads rapidly to onset of lactation (provided that the hypophysis is intact). The mechanism of this reaction is not entirely clear; but some light is cast on it by our recent observation that when, after Caesarian section, the uterus is immediately distended by injection of paraffin, lactation does not occur. In a series of 14 rats all the foetuses were removed by Caesarian section. In eight of these animals both uterine horns were separately ligated with silk at their lower end just above the union, so as to close the lumen. A small incision was then made at the upper end and all the embryos were expelled through this opening. We then filled the uterus with pure paraffin (melting point of 40-42° C.) by means of an ordinary syringe. The temperature of the paraffin just surpassed its melting point at the time of injection, so that it solidified very rapidly in the uterus. Immediately after the uterus was filled we ligated the cranial end of the uterine horns so as to prevent the paraffin from escaping through the incision. Forty-eight hours after this operation the mammary glands were taken from all the animals in this series. While milk secretion had set in in the six rats that were simply subjected to Caesarian section, no trace of secretion was found in the eight rats with distended uteri. From this experiment we conclude that the mechanical factor of distension of the uterus is of considerable importance. We would urge, as a matter of observation, that the apparent tension of the walls of the uterus of the pregnant rat diminishes in the last days of gestation, in spite of the growth of the foetuses. The observation (16) that removal of the foetuses by Caesarian section without removal of the placentae does not induce lactation has been interpreted as an indication that the placenta produces a hormone which in some way inhibits lactation; observations on rabbits (12) and on women (17), in which the foetuses have been aborted very much earlier than the placentae, also seemed to

corroborate this theory, but we feel, in the light of the experiments described, that a purely mechanical explanation is sufficient. In confirmation of this view we have found that implants of mouse placentae fail to inhibit lactation: In a series of six lactating mice we implanted each animal with a whole mouse placenta daily during a period of eight days. Lactation proceeded normally and the mammary glands removed at the end of the experiment showed signs of active milk secretion. It remains uncertain how changes in the state of the uterus can affect the hypophysis. This question has been widely discussed in connection with the production of pseudopregnancy in the rabbit or rat by sterile copulation or by mechanical or electrical stimulation of the vagina and cervix (18, 19), but no satisfactory solution has been found. In our opinion, we are dealing here with a quite similar problem, and this opinion is supported by the fact that injection of paraffin into the uterus of virgin rats inhibits the oestrous changes in the vagina, although it does not reproduce all the phenomena of typical pseudopregnancy, since the mammary glands do not develop. In a series of 20 virgin rats we filled the uterus with paraffin, tying each horn separately at both ends so as to prevent the paraffin from being pressed out into the peritoneal cavity by the contractions of the uterus. These animals were in different stages of the oestrus cycle at the time of operation and it was surprising to see that 17 of the 20 showed full oestrus vaginal smears the day after operation. The vaginal smear then became dioestrous and no oestrus was observed for two to three weeks. We took great care not to touch either the ovaries or the cervix uteri, so as to prevent all possible injury to the gonad or the production of pseudopregnancy by cervical stimulation. Although the condition is suggestive of pseudopregnancy it cannot be identical with it because the mammary glands did not develop and no placentomata formed around the paraffin in the uterus. We feel that these experiments may give a new lead in the experimental study of utero-ovarian correlations, which cannot be elucidated by hysterectomy experiments, since the removal of the uterus as a whole has been found to be practically without effect on the ovary of the rat.

To the general rule that the presence of the hypophysis is essential for lactation there is one important exception. It has been found in the rat by Pencharz and Long (20) and by ourselves (21) that hypophysectomy may be carried out in the second half of pregnancy without producing abortion, and that it delays but does not prevent parturition; the corpora lutea of pregnancy retain their normal structure, although the thecal cells show evidence of deficiency of hypophyseal hormones (22). It has also been shown for the cat (6) and mouse (8) that hypophysectomy need not interrupt pregnancy. Recently we discovered at post-mortem examination that a guinea-pig which had been hypophysectomized eight days previously was pregnant, with a healthy embryo in the uterus. Professor Grosser, of Prag, was kind enough to give the opinion that this embryo was approximately 21-22 days old, from which it appears that the guinea-pig may withstand

hypophysectomy as early as the 13th-14th day of pregnancy without aborting. Serial sections of the base of the brain showed that the pars anterior of the hypophysis had been completely removed, although fragments of the pars intermedia and pars nervosa were still present.

The bearing of these experiments on the present problem is the fact that rats hypophysectomized on the 11th day of pregnancy or later regularly secrete milk for a few hours after parturition (21); similar observations have been made in mice (8). There appears to be no escape from the conclusion that the pregnant uterus or its contents can play the part of the hypophysis in supplying functional stimuli to the mammary glands. We have considered the alternative hypothesis that there exists in some other unknown location in the body a tissue capable of forming prolactin (such as unidentified accessory hypophyseal tissue) but doing so only under the influence of such very strong stimulation as presumably exists at the time of parturition; but we have rejected this view, not only for lack of morphological evidence in its favor, but also because there is no sign of milk secretion in hypophysectomized animals submitted to Caesarian section in late pregnancy (15), or to oöphorectomy after prolonged treatment with anterior-pituitary-like substance (11). Direct evidence that the pregnant uterus is capable of producing a substance with the physiological properties of prolactin is at present lacking, yet it seems impossible to doubt that such is the case. It might be expected *a priori* that the pregnant uterus would assume such a function only at the end of gestation, and we have indeed obtained evidence to show that such is the case. Twenty-two mice were bred at the post-partum oestrus period, so that they were simultaneously pregnant and lactating; the secretion of milk was reduced but not abolished by the presence of pregnancy. It should be mentioned that implantation is delayed and gestation considerably prolonged in lactating mice (23, 24, 25). When these animals were hypophysectomized on the

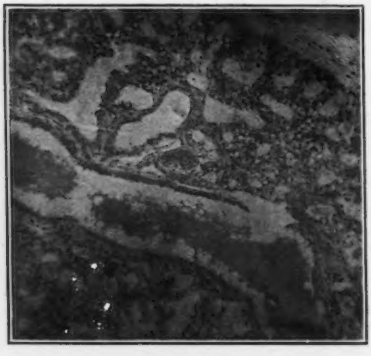

Fig. 1

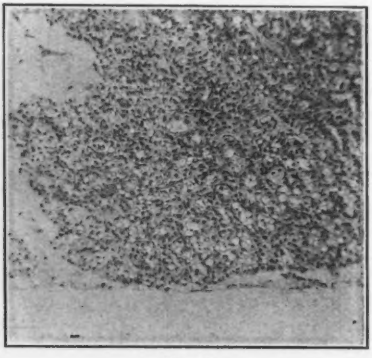

Fig. 2

Figure 1. Mammary gland of a rat both pregnant and lactating, taken at the time of hypophysectomy. Alveoli distended; milk duct full of milk.

Figure 2. Piece of mammary gland taken from same rat two days later. The alveoli have considerably decreased in size, and contain no milk.

15th-22nd day of pregnancy, lactation ceased within 24 hours, in spite of the presence of the pregnant uterus. Milk secretion, however, occurred again for a few hours after parturition, and then permanently ceased. The experiment was repeated on a series of 12 rats which became pregnant again immediately after delivering a litter and were lactating and pregnant at the same time. Figure 1 shows the mammary gland of a rat that was both pregnant and lactating. This gland was taken on the 26th day of the second pregnancy, and the hypophysis was removed at the same time as the mammary gland. (In this connection it should be remembered that lactation delays implantation and thereby prolongs the period of gestation considerably; and, furthermore, that hypophysectomy also prolongs pregnancy, so that many of our animals in this experiment delivered 28-32 days or more after mating.) The alveoli of the gland were distended with milk. Figure 2 shows a piece of mammary gland removed from the same rat two days later. The alveoli are small and empty and show no signs of milk secretion. The litter of this rat obtained no nourishment and had to be given to a foster mother. Figure 3 is a section of mammary gland re-

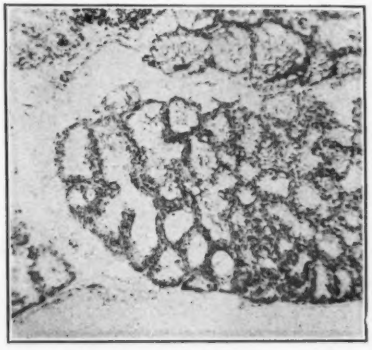

Fig. 3

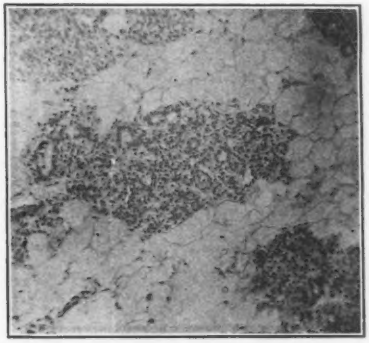

Fig. 4

Figure 3. Piece of mammary gland removed from same rat at the time of delivery. Alveoli are very much distended again, and milk secretion has been initiated.

Figure 4. Piece of mammary gland removed from same rat two days after delivery. Beginning involution of glandular parenchyma. Many fat cells appear in stroma.

moved from the same rat at delivery, which took place two days after the removal of the biopsy shown in Figure 2. Here full lactation is established again and the alveoli are distended with milk. Figure 4 shows involution of the gland two days after the birth of the second litter which died of inanition shortly after birth. We wish to emphasize that, while all the animals of this series were found to have no remnants of pituitary tissue at autopsy upon examination with the lens, the base of the skull was examined histologically by means of serial sections in this and in several other rats and in three animals of the mouse series, and it was found to be free of pituitary tissue, so that the secretion of milk observed at parturition cannot be ascribed to incomplete removal of the pituitary.

It therefore appears that at the end of gestation the pregnant uterus may be a source of functional stimuli to the mammary glands. There is also evidence to be found in the literature, from experiments on species in which pregnancy may continue after oöphorectomy, that the pregnant uterus may also be a source of formative stimuli. It is not now possible to gauge the importance of these functions of the pregnant uterus in animals with hypophysis and ovaries intact. For the maintenance of lactation, it is clear that the hypophysis is solely responsible, and there is every reason to believe that its action is direct. Oöphorectomy does not interrupt established lactation. Since it has been claimed that lactation is not possible in the absence of the adrenals, and even that a special cortical hormone promoting lactation has been demonstrated (26), we have considered the possibility that the action of the hypophysis on the mammary glands might be by way of the adrenals. We have, however, found that adrenalectomy does not stop established lactation with anything approaching the promptness and regularity of hypophysectomy, and have therefore rejected this possibility.

Since hypophysectomy interrupts lactation at any stage, it is clear that the action of prolactin upon the mammary gland is not a "trigger" mechanism but is maintained steadily until weaning takes place. That milk secretion ceases when the young are removed or the nipples are excised is well known, and has been explained in two ways: some have supposed that the accumulation of milk in the glands when suckling ceases is the deciding factor, others have laid weight rather upon the nervous stimulation of the act of suckling. We have already (27) reported a crucial experiment in favor of the latter view, in which we tied off the main galactophore at each nipple of lactating rats, so that suckling continued and indeed was very vigorously maintained in the absence of any yield of milk. In these experiments rapid involution of the glands did not occur. Histological sections showed that milk secretion was present two weeks after the galactophores were cut; hence the mere accumulation of milk inside the gland is unable to stop its secretory activity. The very vigorous suckling which took place in these experiments is not an essential feature; we have found that mere manipulation of the nipples with the fingers may also postpone the involution of the gland after weaning and maintain it in a state of active secretion, although the effect of such treatment is never as marked as that produced by actual nursing.

We have recently extended these studies on the influence of the act of suckling, by experiments on lactating rats in which the galactophores were tied on one side of the body, while on the other the nipples were excised so that suckling did not occur. It was found that the glands did not undergo involution on either side. In a series of eight rats we tied all the main galactophores on one side on the third day of lactation, approaching them through a subcutaneous channel from a skin incision made at some distance from the nipple. Great care was taken not to damage the tissue in the

vicinity of the teat, because in the cases in which this tissue was manipulated the nipple often became necrotic. We then excised all nipples on the other side. Mammary glands taken 14 days after these operations showed that active milk secretion was still present on both sides. From this it may be concluded that the maintenance of milk secretion by suckling is not a purely local reflex, affecting only the glands at which suckling takes place. It is, in fact, extremely probable that the centrifugal part of the arc is at least partly hormonal, and that the act of suckling reflexly evokes secretion of prolactin from the anterior hypophysis, the hormone being, of course, distributed to all mammary glands alike. The observations of Kuramitsu and Loeb (28), who found in the guinea-pig that ligation of one nipple led to involution of that particular gland only, cannot, in our opinion, be cited against this view. These workers tied the nipple of lactating guinea-pigs on one side, leaving that of the other side intact, and found that the gland

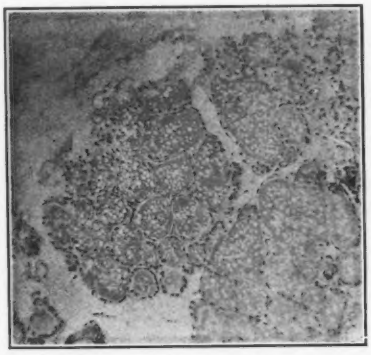

Fig. 5

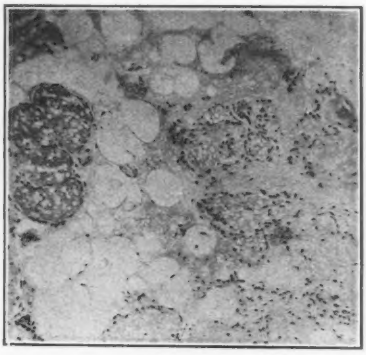

Fig. 6

Figure 5. Mammary gland of a rat three weeks after trancision of all the main galactophores. Alveoli very much distended; glandular epithelium is flat but still well preserved.

Figure 6. Another part of the gland shown in Figure 5. Here degeneration of glandular parenchyma is already very obvious; most of the alveoli are completely destroyed; the stroma and the persisting aveoli contain milk.

on the ligated side involuted in the same way as after weaning, although the animals still nursed their young. The main difference between this experiment and ours is that in our rats no milk could escape from any gland, while in Kuramitsu and Loeb's case one gland was left normal. We therefore repeated our experiments on a further series of 15 rats. In eight of them we tied all the main galactophores on one side and in seven of them we excised all the nipples on one side, the other side being left untouched. All these experiments were performed on the third day of lactation. The results in this series were the same as in the one previously mentioned; that is, milk secretion continued long after the escape of milk to the outside was stopped by trancision of the main galactophore or excision of the whole nipple. Hence the mechanical pressure of the milk which accumulates inside a gland after weaning is certainly not responsible

for the involution of the organ, because normally eight days after weaning involution is well under way and milk secretion has completely stopped, while if suckling is continued the gland is found turgid with milk even as long as three weeks after the elimination of milk through its ducts has been made impossible. After this, however, the pressure of the accumulated milk begins to destroy the gland, and Figure 5 shows a picture of a gland in this stage; the secretory epithelium is already damaged, although the alveoli are still distended with milk. Figure 6 shows another part of the same gland in which the milk infiltrates the stroma and the alveoli show signs of degeneration. Figure 7 is taken from a still later stage: here milk secre-

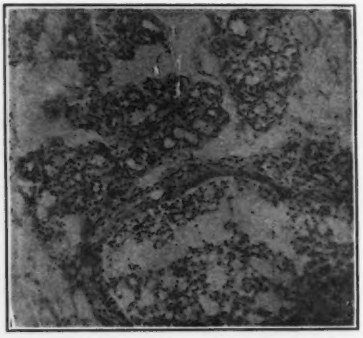

Figure 7. Mammary gland of a rat 25 days after ligature of all the main galactophores. The gland shows beginning involution and numerous leucocytes appear in the milk ducts and alveoli, probably in order to remove the remaining products of secretion.

tion has practically stopped and leucocytes invade the involuting remnants of the degenerated gland. We conclude therefore that—unless the guinea-pig behaves entirely differently from the rat—the experiments of Kuramitsu and Loeb can only be explained by assuming that these authors did not examine the mammary glands during the first stages but only after involution had set in.

Our experiments certainly suggest that the act of suckling reflexly stimulates the hypophysis to secrete prolactin; yet some difficulty arises when we enquire what nervous pathways are involved. Eckhardt (29) in 1855 cut all the nerves of the udder in goats and saw no change in the amount of milk secreted after the operation; and this experiment has been confirmed (30, 31). Temporary increases in milk secretion after stimulation of the sensory nerves of the teat in goats (32) or of the external spermatic nerve in dogs (33) could not be obtained in the guinea-pig (34) and are in any case probably due to contraction of the musculature of the milk cistern (35). Basch (36, 37), who reviews the earlier literature in detail, transplanted a piece of mammary gland under the skin of the back, in a dog, and found that the transplant secreted milk after parturition; similar results have been obtained in rabbits (38), and milk secretion may occur in

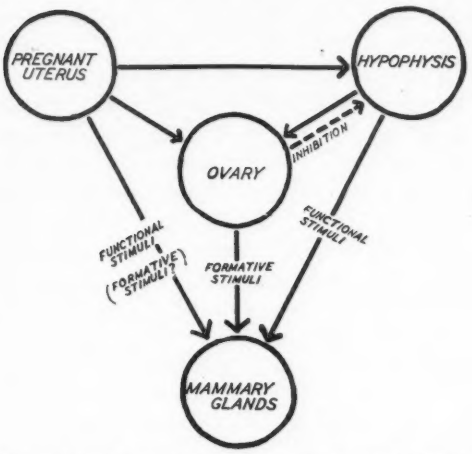

Figure 8. Diagram showing mechanism of hormonal control of mammary glands.

transplantable mammary adenomas, after parturition, in rats (39). These last results clearly support the view that the centrifugal part of the mechanism of mammary stimulation is hormonal. The difficulty is rather in locating the centripetal pathway, in the light of the denervation experiments quoted, especially since Goltz and Ewald (40) were able to remove almost the entire spinal cord in dogs without interfering with either pregnancy or lactation, and since Cannon (41, 42) in the cat and Bacq (43) in the rat found that while sympathectomy might prevent lactation it did not do so immediately nor invariably, and Basch (36) found in dogs and rabbits that the effect of extirpating the coeliac ganglion in inhibiting lacta-

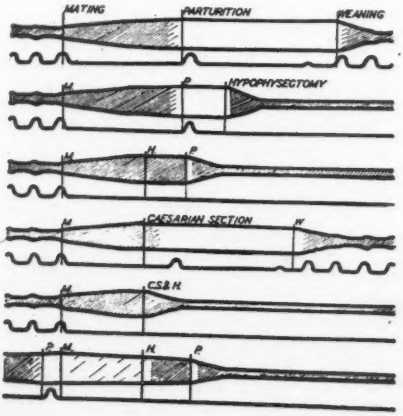

Figure 9. Diagrams showing development and secretion of mammary gland under various experimental conditions. Upper section of each diagram shows development of mammary gland; the shaded parts presenting the resting, the white part the lactating condition. The line in the lower section of each diagram shows the oestrus cycles.

tion was obtainable only when the operation was performed very shortly after parturition.

The third question raised in the introductory paragraph relates to the inhibition of oestrus during lactation. It is known that this inhibition cannot be prolonged to the same extent as can lactation itself, by provision of fresh litters (44), and it is also known that the lactation-dioestrus is not seen if the litter is of much less than normal size; for example, if only one or two young are being suckled; Parkes (45) suggests that it is for this reason that oestrus cycles are not interrupted by lactation in the guinea-pig. These facts in themselves suggest a connection between the secretion of milk and the inhibition of oestrus; we feel that this inhibition is also a nervous mechanism, because of our recent observation that in the animals with ligated galactophores, suckled but yielding no milk, oestrus did not

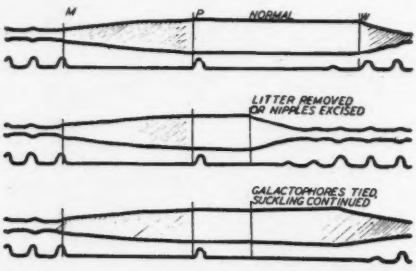

Figure 10. Diagrams showing the effect of trancision of main galactophores and suckling on the development of the mammary gland. As in Figure 9, upper section of each diagram shows development of mammary gland; lower section, oestrus cycles.

occur; in fact, the vaginal smears were of most marked dioestrous type, usually containing leucocytes only. We believe accordingly that the act of suckling reflexly affects the anterior hypophysis, so that the latter continuously produces prolactin and at the same time modifies its activity towards the ovaries so that the corpora lutea of the post-partum ovulation long retain their healthy structure and active function (46), while further ovulation and the phenomena of oestrus are inhibited. It is, however, entirely possible that important links in this series of correlations between the uterus, the ovaries, the hypophysis, and the mammary glands remain to be discovered, and that the whole network is more complex than we are, at present, justified in assuming it to be.

SUMMARY

1. Established lactation was rapidly and invariably terminated by hypophysectomy in six mice and in a large series of rats; lactation was also terminated by hypophysectomy in 22 mice and 12 rats which were simultaneously pregnant and lactating.

2. In another experiment hypophysectomy was carried out on 24 rats and 6 mice, in the latter half of gestation, without leading to abortion. A

guinea-pig hypophysectomized on the 14th day of pregnancy carried a healthy foetus when sacrificed eight days later.

3. All the mice and rats hypophysectomized during pregnancy secreted milk for a few hours after parturition.

4. In 20 virgin rats, distension of the uterus with paraffin caused prolonged dioestrus without the mammary development typical of pseudopregnancy.

5. Caesarian section late in pregnancy induced lactation in 16 rats, but not in 6 others in which hypophysectomy was also carried out, nor in 8 others in which the uterus was distended with paraffin after removal of the foetuses.

6. Rapid involution of the mammary glands did not occur in 7 lactating rats in which all galactophores were tied but suckling continued. The nervous stimulus of suckling at the nipples of certain glands maintained active secretion in neighboring glands not being suckled.

7. Lactation dioestrus was maintained by the act of suckling in those rats in which escape of milk was prevented by ligation of all galactophores.

8. The correlations between the pregnant uterus, the ovaries, the hypophysis and the mammary glands are discussed in the light of these and other findings. It is suggested (a) that the pregnant uterus may, like the hypophysis, supply functional stimuli to the mammary glands, (b) that mechanical distension of the uterus affects hypophyseal function, and (c) that the act of suckling affects hypophyseal function, especially in maintaining the secretion of prolactin.

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OVARIAN STIMULATION BY ADRENAL EXTRACTS†

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Although there seems to be a close relationship between the activities of the adrenal glands and the gonads, attempts to promote gonad stimulation by means of adrenal substances have not given consistent results. Nice and Shiffer (1931) produced precocious sexual maturity in young rats by means of adrenal transplants while Claus (1931) obtained similar results in mice with alcohol soluble fractions of adrenal cortex. Kaplan (1932) reported both positive and negative results from each of several different types of preparations. Cortical adrenal extracts, prepared by the method of Swingle and Pfiffner, have been tested by Corey and Britton (1931 and 1933), Connor (1931), and Gaunt and Parkins (1933). The former reported production of precocious maturity in rats, while the latter two failed to confirm this result.

The gonadotropic hormones as obtained from the anterior pituitary, placenta, and blood and urine of pregnancy are insoluble in higher concentrations of acetone and ethyl alcohol. It seems logical, therefore, that attempts to determine the presence of gonad-stimulating substances in the adrenal glands might best be undertaken by methods similar to those used in extracting these substances from other sources.

PROCEDURE

Whole adrenal glands from horses,‡ collected at various times from July to January, were extracted according to the procedure of Fevold, et al. (1933) for the preparation of gonadotropic substances from the anterior pituitary. The extracts used in this study were prepared from acetone desiccated adrenal powder from pregnant and non-pregnant mares and from geldings. Similar control extracts of acetone desiccated blood, blood serum, ovaries, and livers from horses were prepared for comparison. The two following types of extracts which were used will hereafter be referred to by number only: (1) active substance soluble in 50 per cent aqueous pyridine, 33⅓ per cent acetone, and which contains both follicular-stimulating and luteinizing substances; (2) active substance soluble in 50 per cent aqueous pyridine, 33⅓ per cent acetone, 60 per cent ethyl alcohol, and contains primarily the follicular-stimulating substance.

A total of 82 female rats 21-25 days old were used for test animals. Each was injected subcutaneously twice daily during a period of five days

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*National Research Fellow in the Biological Sciences.

‡Adrenal glands were made available through the courtesy of Chappel Bros., Inc., Rockford, Ill.

and was killed on the sixth day. The ovaries were weighed and serial histological sections were prepared of both ovaries and tubes for a detailed study of the degree and type of stimulation of the ovaries and determination of presence or absence of tubal ova.

EXPERIMENTAL RESULTS

The preliminary extracts (No. 1) from two different lots of pregnant mare adrenals produced unexpected increases in ovarian weights of the test animals. Ovaries weighing as much as 149 mg. resulted from administration of 3 gm. equivalent of the dried powder. A consideration of the mares from which these glands came seemed relevant because extracts from a third lot of pregnant mare adrenals produced ovaries averaging only 22 mg. in weight when a 3 gm. equivalent dose was administered. Mares furnishing the first two lots carried foals from 2 to 18 cm. in crown-rump length, while the foals from the group furnishing the third were from 20 to 25 cm. in length. Tests of the blood serum from these three groups of mares showed the presence of gonad-stimulating substance but the serum from the third group was less active than the other two which is in accord with the findings of Cole, et al. (1930 and 1931). This suggested that at least a part of the gonadotropic effect of these adrenal extracts was due to the blood which remained in the excised glands.

The adrenals and blood of non-pregnant mares and of geldings were tested to exclude the possibility of gonad-stimulating action of the residual blood in the glands. The rats used in preliminary tests of the adrenals of geldings had small ovaries although the vaginas were open on the sixth day. Histological examination of these small ovaries showed that definite stimulation had occurred as shown by presence of large follicles or corpora lutea. Weights were taken of the ovaries from a group of 20 control rats for comparison with those of the test animals and they weighed from 9.2 to 13.5 mg., with a mean weight of 11.9 mg. Histological examination of these ovaries showed no follicles to be greater than 650 microns in diameter.

Eight different lots of adrenals from geldings and non-pregnant mares were tested (Method No. 1) and each gave positive ovarian stimulation (Table I). Ten of the 20 rats showing a positive ovarian reaction had ovu-

TABLE I

EXTRACTS OF GELDING AND NON-PREGNANT MARE ADRENALS

No. Rats	Adrenal Lot No. and Source	Average Dosage, Gms.*	Weight of Stimulated Ovaries, Mgm.		No. of Positive Animals	
			Average	Range	Ovarian Stimulation	Ovulation
4	1 F	5.	23.6	14.0–35.9	4	3
2	2 F	5.	9.0	.....	1	0
4	3 F	3.5	10.8	8.2–12.9	3	1
3	4 F	6.7	16.5	12.0–18.9	3	2
1	5 F	7.	15.2	.....	1	1
4	6 M	5.	12.5	7.8–18.2	3	2
2	7 M	5.	13.9	13.4–14.4	2	1
3	8 M	6.7	14.7	13.5–15.7	3	0

*Dosage is in grams equivalent of dried adrenal powder.

lated, and in the stimulated ovaries which had not ovulated, there were two or more large follicles (750-1050 microns in diameter), which ranged from a total absence of luteinization to the formation of almost solid corpora lutea atretica. Some of the more normal appearing ova in these follicles had vesicular nuclei and others showed the presence of the first polar body and the second meiotic spindle.

From one to five ova were observed in the fallopian tubes of the rats which had ovulated. Histologically some of these seemed perfectly normal and in many instances were enmeshed in a cluster of follicle cells. The appearance of the ruptured follicles from which these eggs came gave evidence that the time of ovulation was recent. Other eggs appeared to be in different stages of degeneration. Attention is called to one interesting case in which four tubal ova were observed although the vagina had not opened.

These experiments showed that gonad-stimulating substances could be obtained not only from the adrenal glands of pregnant mares but from non-pregnant mares and geldings as well. The presence of such factors could not be accounted for by the blood which might have been residual in the excised glands for extracts of non-pregnant mare serum were administered in doses of 12.5, 20.0, and 28.5 cc. equivalent without a positive response. Non-pregnant mare blood in doses of 60 and 140 cc. equivalent were likewise negative and administration of gelding serum extract in 22.5 and 40 cc. equivalent doses had no effect on the immature rat ovaries. Furthermore, extracts from a highly vascular and non-specific organ, the liver, of geldings and non-pregnant mares produced no ovarian response when administered in dosages of 5 and 10 gm. equivalent of the powder. Some of the blood and liver samples were from the same horses whose adrenals produced positive ovarian responses.

Although the presence of the gonad-stimulating factors in the adrenals could not be attributed to the residual blood in the glands, the question was not answered as to whether the factors were secreted by the adrenals or whether they were concentrated from the blood and stored there. It seems that if the gonadotropic substances were due to a concentration of the anterior pituitary or anterior pituitary-like hormones, they should also be obtainable from other organs specifically affected by them, for example, the ovary. However, extracts (Method No. 1) of ovaries (those having follicles and those with corpora extracted separately) of non-pregnant mares in doses of 10 gm. equivalent produced no ovarian response in the test rats.

The incidence of ovulation in the ovaries stimulated by the adrenal extracts (No. 1) of geldings and non-pregnant mares was high enough to attract attention (10 of 20). All of the ovaries which had ovulated were small and the question arose as to whether similar extracts of other tissues known to contain gonad-stimulating substances would produce ovulation when injected so as to produce ovaries of equivalent size. In other words, is there a qualitative difference between the gonadotropic substance

found in the adrenal and that found in other tissues? Fairly equivalent weight ovaries stimulated by similar extracts (Method No. 1) of adrenals of pregnant mares gave ovulation in one animal of five that were treated (Table II) and extracts of horse pituitaries one of six, or a total for the

TABLE II

OVULATION PRODUCED BY ADRENAL AND PITUITARY EXTRACTS

No. Rats	Material Extracted	Extraction Method	Ovarian Weight, Mgm.		No. Rats Ovulating
			Range	Average	
12	Adrenal—Non-pregnant mare	1	8.2–35.9	16.5	7
8	Adrenal—Gelding	1	7.8–18.2	13.7	3
5	Adrenal—Pregnant mare	1	13.1–24.5	18.9	1
6	Pituitary—Horse	1	12.0–27.0	16.0	1
6	Adrenal—Prenant mare	2	17.2–39.8	28.7	6
4	Pituitary—Horse	2	20.0–30.0	25.5	4

two experiments of two rats ovulating in the 11 rats used. However, extracts of adrenals from pregnant females and horse pituitaries prepared by Method No. 2 which eliminates much of the luteinizing factor gave ovulation in all rats tested (10 animals). Although the ovarian weights above are not entirely comparable and the data are insufficient to be conclusive, it might suggest that the proportion of luteinizing substance to follicular-stimulating hormone in the extract is of importance with regard to ovulation. The higher incidence of ovulation produced by extracts of non-pregnant female and castrated male horse adrenals over similarly prepared extracts of the pituitary and adrenals of pregnancy might be attributed to a lower degree of luteinizing activity in relation to follicular-stimulating activity.

DISCUSSION

The evidence that a gonadotropic substance is present in the adrenal gland rests on the fact that positive ovarian responses were obtained from extracts of 12 different lots of horse adrenals. It was found that extracts of the adrenals of mares in certain stages of pregnancy were more potent than those prepared from the adrenals of non-pregnant mares. This may be due to the gonad-stimulating hormones normally present in the residual blood of the adrenals of pregnant mares (Cole and Hart, 1930). This, however, cannot account for the activity of the extracts prepared from the adrenals of non-pregnant mares and of geldings as preparations equivalent to large quantities of the blood of such animals had no noticeable effect on the ovary. Whether the adrenals of these animals secrete the active principle or the hormones of the pituitary are present in the blood in small amounts and are concentrated in the adrenals is an open question. If these hormones are concentrated it should be possible to obtain active extracts from other organs which are directly stimulated by them. Extracts of mare ovaries, however, gave only negative results.

Another demonstration of the gonadotropic activity of adrenal extracts was the instances of ovulation. Ovulation occurred more frequently in the rats treated with extracts prepared from adrenals of geldings and non-pregnant mares than those from pregnant mares, and in all cases the ovaries were small. The size of the ovaries, however, does not seem to be the only determining factor for ovulation as ovaries of similar size produced in six animals by pituitary extracts (No. 1*) showed only one ovulation. It seems that ovulation may depend more directly on a proper balance between the follicular-stimulating and lutetinizing activities and if too much of the latter is effective the ova are entrapped by rapid luteinization. When the amount of luteinizing hormone in the extracts of pituitaries and pregnant mare adrenals was decreased by employing Method No. 2, ovulation was produced in each of the ten animals used (Table II).

SUMMARY

Extracts of eight different lots of adrenals from non-pregnant mares and geldings were prepared by pyridine extraction and tested on 21 to 25-day-old female rats (lots of 1 to 4 rats per test) for gonadotropic activity.

Positive ovarian responses as indicated by presence of large follicles or corpora lutea were obtained from extracts of each lot of adrenals and ovulation occurred in fifty per cent of the responding test animals.

Similarly prepared extracts of whole blood, blood serum, liver, and ovaries from the above classes of horses failed to produce ovarian responses even when administered in comparatively large doses.

The adrenal extracts which effected the greatest increase in ovarian weight of the test rats were prepared from mares in those stages of pregnancy during which their blood had the greatest gonad-stimulating activity. It was shown, however, that gonadotropic responses could be obtained from extracts of adrenals from non-pregnant mares and geldings whose blood did not show gonad-stimulating activity.

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*More recent experiments have indicated that extracts of this type from different batches of horse pituitary may vary in their ability to produce ovulation.

EFFECTS OF COD-LIVER OIL ON BASAL METABOLISM AND ON THE THYROID GLAND

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Numerous experiments have shown that therapeutic doses of cod-liver oil cause toxic effects and organic changes of a regressive type. Agduhr (1) demonstrated that cats and dogs showed no sign of heat when doses of 1 cc. to 5 cc. of cod-liver oil per kg./day were added to the basal diet beginning at the age of one month and continuing for one year. The number of red blood corpuscles was decreased simultaneously with a fairly steady increase of the relative haemoglobin value. The spleen was abundantly supplied with blood pigments, a sign that the disintegration of red blood corpuscles was above the normal. Histological changes in different organs chiefly of a regressive nature were found but no mention was made of the thyroid gland. The weight curves of the mice as well as the microscopical examination of their organs showed many disturbing alterations.

In 1925 Slagswold (2) noted poisoning among cattle by cod-liver oil while rodents thrived on the same oil. Norris and Church (3) point out that the toxic effect of large doses of some cod-liver oils is not due to hypervitaminosis due to excess of vitamins A and D. Continued small doses of isoamylamine in amounts which may be found in cod-liver oil produce paralysis, convulsions, and lack of growth; the toxic effect may be prevented or cured by added yeast. Harris and Moore (4) report that results obtained have been distinguished by a remarkable regularity in the retarding action of the vitamins A and D concentrates upon growth rates. Riddle and Baucher (5) have shown that a high value of metabolism in pigeons shows at the same time a higher haemoglobin and erythrocyte value. The opposite effect is produced with a low metabolism.

Since large doses of cod-liver oil have, as a rule, been followed by a decrease in the number of red blood corpuscles and marked regressive tissue changes, it was decided to run basal metabolism determinations and to study the thyroid gland since this organ has a definite function in basal metabolism.

PROCEDURE

Fifty-seven male and female rats were used in this investigation. The diet consisted of a well-balanced grain ration, supplemented with green food and milk. In addition to the basal diet, 27 animals were given from 1 cc. to 5 cc. of cod-liver oil (Squibb's) per kg./day. Of the 30 animals which were used as controls, 10 received corn oil, 10 viosterol* (Mead John-

*Irradiated Ergosterol (Viosterol) was generously furnished by Mead Johnson & Company, Evansville, Indiana.

son), and 10 cod-liver oil minus vitamin A. Heat and oxidation were used for the removal of vitamin A.

The basal metabolism was measured by means of Marine's modification of Haldane's open circuit apparatus (6). Tests were run until a constant level of metabolism was reached and maintained for several days before any results were included in our data. A fasting period of 20 hours preceded each metabolism test. The basal metabolism determinations were run every other day on each animal throughout the investigation which extended over a period of six weeks. The animals were then killed for tissue study.

RESULTS

No change in basal metabolism was produced in any of the animals during the investigation. When sections of the thyroid glands were studied at the termination of the basal metabolism tests, marked changes were noticed only in the glands of the rats that had received normal cod-liver oil. The thyroid glands were nearly depleted in acinar colloidal content. The thyroid glands of the 30 control rats showed no deviation from the normal when compared to the glands of a group of animals that had received only the normal basal diet.

Figure 1. (Rat 63). Normal thyroid gland.

Figure 2. (Rat 69). Section of thyroid gland in which very little or no colloid can be seen in the acini. This was the typical picture of all the thyroid glands of rats which had received cod-liver oil.

SUMMARY

In 27 rats that received 1 to 5 cc. cod-liver oil per kg./day a decided change was produced in the thyroid gland, namely, a depletion of the colloidal content of the acini. Three control groups of ten animals each received, respectively, corn oil, viosterol and cod-liver oil from which the vitamin A was removed by heat and oxidation. In these the thyroid was not affected.

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STUDIES OF THE ADRENAL GLANDS IN HEALTH AND DISEASE

I. DISEASES OF THE ADRENAL GLANDS AS REVEALED IN 25,000 AUTOPSIES†

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INTRODUCTION

Since the function of the adrenal glands is so imperfectly understood, all data relating to them in health and disease are important as they may bear on the elucidation of the rôle of these glands in the organism. In order to understand their physiology better, it is essential that we know more of their anatomy and histology, with particular reference to the types of cells present, their functions and their hormonal products. Furthermore, it is important to ascertain whether or not the function of similar types of cells found in various zones are identical and if their grouping in these zones has biological significance. In disease we must learn the nature of the pathological processes in the adrenals, the changes in the glandular cells, the resulting derangements of function together with the associated clinical pictures.

DEVELOPMENT

It is definitely known that, from a phylogenetic standpoint, the adrenal gland consists of two distinct organs. In lower vertebrates the cortex and medulla are anatomically separate structures. In mammals the medullary tissue grows into the cortex during fetal life and becomes encapsulated by it. In amphibians an intermediate process is noted; the suprarenal glands consist of interrenal tissue, with islands of chromaffin cells scattered throughout. In man the cortex develops from the celomic mesoblastic layer, the medulla from ectodermal nervous tissue. As the medullary elements become united with the cortical tissue, fragments of tissue (chiefly cortical) may split off to form accessory adrenal glands; these structures have now been found throughout the abdominal cavity and in the ovaries and testes; their presence or absence is a matter of individual variation. Their number and size vary greatly with the age of the person. According to Jaffe, they are found in about 50 per cent of infants if carefully searched for; in adults, demonstrable accessory tissue is much less commonly found. These accessory glands are of great clinical significance, since the duration of life in Addison's disease may depend on their presence or absence, and

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*From the Samuel Bell, Jr., Laboratory.

on their ability to undergo hypertrophy. They are also of significance in the study of the effects of experimental suprarenalectomy.

HISTOLOGY

The adrenals are extremely vascular organs, consisting of cortex and medulla. The latter contains ganglion cells and fibers of the sympathetic system. The whole is enclosed in a capsule of fibrous tissue of moderate density.

The cortex is composed of palely staining, rather large cells. These, from their architectural arrangement, subdivide the cortex into three zones with no sharp differentiation, one merging into the other. With ordinary stains the cells of the different zones differ—(1) in their lipoid content; (2) in their staining reactions, cells of the zona glomerulosa tending to be basophilic while those in the zona reticularis are acidophilic, granular, pigmented and more irregular in their arrangement. The widest of the three zones, zona fasciculata, is formed of columns of cells, the free border being apposed, thus leaving a potential lumen, their bases resting on a thin reticulum, supporting fine capillaries.

The architecture of the medulla is much less uniform. The cells are scattered in irregular masses of varying size throughout the middle of the gland but are more concentrated in the center. The cells appear delicate; are somewhat granular, polygonal or round; and are arranged in sheets and anastamosing cords surrounded by capillaries and blood sinuses. Scattered here and there, one may see single or grouped ganglion cells and occasional nerve fibers.

The arteries to the adrenal enter the capsule and there split up into three distinct systems, one supplying the capsule itself, a second the cortex and a third entering the medulla without branching. The cortical and medullary arterioles break up into capillaries in close contact with the parenchymal cells, form sinusoids and eventually anastamose to form the rather large central veins, which are surrounded by a thick wall of smooth muscle, out of proportion to the size of the vein. The longitudinal muscle bundles are extremely prominent.

PHYSIOLOGY

Our present understanding of the physiology of the adrenal glands is extremely imperfect. Brown-Séquard in 1856 first reported the results of extirpation of the adrenal glands in the experimental animal. He found that with unilateral extirpation the animals survived about 25 hours, whereas with bilateral extirpation they lived but 10 hours at the most. He concluded, therefore, that death was the result of a toxin which accumulated in the absence of a sufficient amount of functioning adrenal tissue. The fact that the adrenal glands are essential to life has been proven beyond question of doubt.

The symptoms which follow experimental adrenalectomy are well known, and have been fully described by many writers, notably Stewart and Rogoff. For a short time following the removal of the second gland, the animals are apparently normal and do not suffer any inconvenience until shortly before death; then marked anorexia develops, sometimes associated with vomiting and diarrhea. Muscular and nervous irritability is increased; coma or convulsions, or the so-called "mad fits" may occur. The pulse rate and temperature frequently fall. At necropsy, congestion of the abdominal viscera is noted; ecchymosis or ulceration in the intestinal and gastric mucosa is not infrequent. The blood appears to be concentrated; focal necrosis and degeneration may be seen in the liver and kidneys. Attempts to prolong indefinitely the lives of these animals have not been successful until quite lately; however, intravenous administration of a physiologic solution of sodium chloride has been shown by Stewart and Rogoff to have a beneficial effect in prolonging life and in the relief of symptoms. These findings have also been adequately confirmed by many investigators.

The question has arisen, however, as to which of the phylogenetically distinct portions of the adrenal glands in man is necessary to life. The evidence, both experimental and clinical, points definitely to the conclusion that destruction of the cortex is incompatible with life and that its gradual destruction is probably responsible for the symptoms which Addison described.

The history of the development of knowledge concerning adrenal extracts is an all-important chapter in the study of Addison's disease. Vulpian (1856), who first recognized the chromaffin system, demonstrated an adrenal extract which became greenish when ferric chloride was added; Arnold (1866) prepared a yellowish alcoholic extract which darkened to red on warming and exposure to air.

The demonstration of the physiologic properties of medullary extracts (Oliver and Schaefer, 1894) was followed by the work of von Furth and Abel. Abel prepared a crystalline benzoyl derivative of an unknown substance from the adrenal medulla. This work was followed by the actual isolation, crystallization, and purification of the compound by Takamine and Aldrich. The name "epinephrine" was suggested for this substance by Abel. Jowett (1904) determined its structural formula, and Stolz effected its synthesis the same year. It is known to consist of two essential parts, the benzene ring and the side chain of two carbon atoms attached to the ring. On the ring are also two hydroxyl groups, one of which is para to the side chain. On the side chain are two groups, a hydroxyl on the first carbon, and a methyl amine group on the second carbon. It is obvious that many closely related derivatives can be prepared which differ from epinephrine in minor details only.

Few substances have had a more profound effect on the practice of medicine, and an enormous literature has grown up in regard to its physio-

logic and pharmaco-dynamic properties. The function of the medullary substance in health and disease is not fully understood; Cannon's theory that the secretion is called into use in emergency is perhaps the one most generally accepted. Epinephrine is known to be present in the circulating blood of normal subjects and it is said to be absent in Addison's disease. The lassitude, low blood pressure and gastro-intestinal irritability that are characteristic of Addison's disease have been attributed, without good cause, to failure to produce epinephrine. In view of the experiments which show the cortex to be the portion of the gland essential to life, it is apparent that the relation of the formation and production of epinephrine to Addison's disease must be held sub judice. However, the therapeutic use of epinephrine in this condition gives sufficiently good results in certain cases to make one cautious in disregarding entirely the significance of loss of epinephrine in the production of addisonian symptoms.

The adrenal glands apparently have an important bearing on sex function as evidenced by the marked changes in the sex organs encountered in tumors arising in the cortex. The anatomical and physiological effects are dependent to a certain extent on the time at which the tumor develops. Congenital tumors may lead to pseudohermaphroditism; tumors of infancy and childhood to pubertas praecox; and tumors in the adult to virilism and hirsutism. Removal of such tumors may result in complete disappearance of all abnormal sex manifestations. However, the particular adrenal cell, if adrenal in origin, responsible for these effects has not been definitely identified nor has the hormone concerned been isolated.

The present status of cortical extracts deserves mention, since it is possible that from studies with these substances the cure or control of the symptoms of Addison's disease will come. Early experiences with the cortical extracts were almost wholly unsatisfactory. More recently, however, encouraging results have been obtained. Rogoff and Stewart prepared an extract which definitely prolongs the lives of adrenalectomized animals, and they also obtained some definitely beneficial clinical results with this substance. Hartman and his collaborators prepared an extract for which they proposed the name of "cortin." Adrenalectomized animals treated with this preparation survived an average of 27 days or longer, compared with the survival of 5 to 6 days of the control animals. At a recent meeting of the Society for the Study of Internal Secretions, Hartman showed one animal which had survived 170 days. Swingle and Pfiffner, in March, 1930, announced that they had isolated a substance which prolonged the lives of adrenalectomized cats indefinitely. Following the administration of this substance, no evidence of the removal of the adrenal gland could be obtained. The animals behaved normally in every respect and their appetites remained normal. Since this result has been obtained in so many of their animals, doubt cannot exist concerning the efficacy of the cortical hormone. These workers have commented particularly on the effect of the cortical extracts on anorexia and loss of weight and on the

decrease of plasma volume and haemoconcentration of adrenalectomized animals. They found that untreated animals showed gastro-intestinal symptoms to a marked degree, but on resumption of treatment there was marked increase in appetite and weight. They have also found evidence which would seem to show that there is a hormone of the adrenal cortex which has a profound effect on metabolism as a depressor, and some clinical evidence has already accumulated to indicate that this hormone may prove of value in the treatment of hyperthyroidism, an idea championed by Marine. He has demonstrated an increase in metabolism following experimental injury to the adrenal cortex, and has also shown an elevation of metabolism in the new-born which corresponds chronologically to the period during which the adrenal cortex undergoes its normal process of involution. Finally, he has used fresh adrenal extract with benefit in hyperthyroidism. Clinical studies with the extract of Swingle and Pfiffner in cases of hyperthyroidism which are being carried out by some workers in New York, at Johns Hopkins University, and at The Mayo Clinic are adding evidence in support of this view.

One feature receiving unusual emphasis at the present moment is the control exercised by the adrenal gland on blood and plasma volume. Although low blood volume was reported by us in the crises of Addison's disease, little attention was given to this matter until the work of Swingle and Pfiffner, in which they claimed that the control of blood volume was a primary function of the adrenal gland. Through the work of Loeb and others this was shown to be effected in part through control of the sodium ion of the plasma. This ion is concerned with the hydrophylic properties of plasma proteins, and, therefore, more or less directly with blood volume. This experimental work is in keeping with the claims of Rogoff and Stewart in animals and of ourselves in Addison's disease, as to the tremendous value of sodium chloride in control of the symptoms resulting from hormonal deficiency.

Two other substances isolated recently from the adrenal gland are of interest physiologically. Koehler has prepared an epinephrine-free extract which he claims will affect metabolism, blood pressure, and the oxygen deficit after exertion by patients suffering from certain types of asthenia. Recently Szent-Györgyi isolated a compound from the adrenal cortex, which is definitely specific for that organ. This compound, hexuronic acid, deserves attention for its remarkable reactivity and high reducing power. According to Szent-Györgyi it is a catalyst of certain oxidation systems.

Without discounting the value of studies on extirpation of the gland and on the preparation of glandular extracts, it must be said that the exact physiologic functions of the adrenal gland in the intact animal are uncertain. Our exact knowledge of the physiology of the adrenal glands can be expressed in the following statements: (1) The cortex of the gland is essential to life. (2) The medulla of the gland, although apparently not a vital

organ, secretes a substance which is normally present in the blood stream and which has powerful pharmacodynamic properties. (3) The cortical hormone is effective in removing all the clinical manifestations of hormonal deficiency in Addison's disease. (4) This hormone is in some way concerned with the control of blood volume and of the sodium ions of the plasma. (5) Certain tumors arising in the cortex are in some unknown way concerned with sex function. Of the multitude of other functions suggested, few rest on adequate grounds.

As a preliminary step in these studies, we have attempted to ascertain all the pathological lesions of the adrenal glands as indexed in the files of the Laboratories of the Philadelphia General Hospital. It covers all the necropsies performed in this institution since 1867; 5,000 post mortems prior to 1900; 6,000 between 1900 and 1919; and 14,000 between the years 1919 and 1933. Unfortunately we have no figures relative to hospital admissions extending back to 1867, but from 1890 to 1932, inclusive, there have been 568,567 admissions to this institution. Thus this study reviews the grossly visible pathology found in the adrenal glands at necropsy in this institution.

All the available slides of the adrenals have been carefully examined histologically. It is to be noted, however, that these sections were cut in a routine manner by numerous visiting pathologists and assistants in the laboratories, were stained in a routine manner by hematoxylin and eosin, and that no special stains had been used in an attempt to differentiate types of cells in various lesions encountered. In our study we have had no way of knowing from which particular portion of the adrenal the sections were taken nor in what plane the sections were cut. This has made it difficult at times to confirm the gross diagnoses of hypertrophy or atrophy of either cortex or medulla.

Two interesting and outstanding facts are immediately apparent. The first is the paucity of adrenal lesions noted. It is surprising that in a series of more than 25,000 necropsies (Table I) the adrenal was found definitely abnormal in only 925 instances* (3 per cent) and that in only 511 (2 per cent) was the pathology considered such as to warrant histological examination. In some instances the post mortem descriptions of the adrenal were too incomplete or too indefinite to warrant acceptance of the gross diagnosis, and inclusion in this study. It is obvious that in the vast majority of cases, until 12 or 15 years ago, the adrenals were apparently more or less ignored at autopsy. Routine and detailed studies are essential to accurate knowledge of the rôle played by the adrenals in general disease. Equally striking is the decreasing incidence of certain lesions. Certain pathologic lesions of the adrenals have decreased markedly within the past few decades. This is most notable in relation to amyloid infiltration and to tuberculosis.

*We have not included in the list of lesions so called "cystic degeneration," which is now recognized as a post mortem change.

TABLE I
GENERAL DISTRIBUTION
P. G. H. 1867-1932
DIAGNOSED

Type of Lesion	Grossly	Histologically
Inflammation	272	246
Degeneration	184	45
Disturbances of lipoid content	109	59
Infiltration	62	26
Hemorrhage	32	13
Hypertriphy and atrophy	47	20
Neoplasma—		
Metastatic	87	43
Primary	116 (124)?	56
Miscellaneous	10	3
Abnormalities	6	0
Total	925	511

INFLAMMATION

Table I shows the distribution of lesions observed in this study. As will be seen the commonest lesion noted in the adrenal is inflammation. These cases are subdivided in Table II. The striking feature in the examination of this lesion is that only three cases showed definite evidence of acute inflammation as shown by infiltration with polymorphonuclear leucocytes. This becomes more surprising when the extreme vascularity of the entire adrenal gland is considered. Many cases were diagnosed grossly as acute adrenalitis but histological examination failed to support this. Such glands were encountered in cases of septicemia and bacteriemia but sections failed to show infiltration with pus cells although certain adrenals showed bacterial emboli in some of the larger vessels. However, in the absence of a surrounding acute inflammatory reaction we considered these were of post mortem rather than of ante mortem origin. Many clinicians believe that these glands are subject to infection in febrile diseases especially in influenza and bronchopneumonia and that this results in temporary depression of adrenal function. Evidence in these connections is sorely needed. Likewise both pathological and clinical data are lacking relative to the adrenal glands in the diseases of other endocrine glands.

TABLE II
INFLAMMATORY LESIONS
P. G. H. 1867-1932
Listed, 272. Studied, 246

Acute	3
Chronic (fibrosis)	188
(Associated cardiorenal vascular 123)	
(White 118—Black 69)	
Tuberculosis	55
Total	246

Chronic adrenalitis and fibrosis are tabulated in Table III. Histologically chronic adrenalitis was diagnosed when there was a diffuse or focal infiltration with lymphocytes and plasmacytes in either cortex or

medulla. The presence of cellular infiltration in the cases of chronic adrenalitis led us to believe that this condition was active and progressive. Fibrosis, as the term indicates, was characterized by an increase in fibrous tissue in both the medulla and cortex. It was considered passive rather than active and may possibly have followed a chronic or subacute adrenalitis. In both conditions associated arteriosclerotic lesions were encountered but infrequently. The discrepancy in average age of the two conditions may well be accounted for by the fewer number of cases of pure fibrosis examined.

TABLE III
CHRONIC ADRENALITIS AND FIBROSIS
P. G. H. 1867-1932

	Number	Average Age	Age Limits	Associated Diseases
Chronic adrenalitis	160	54	17–87	C. R. V. 105 66%
Fibrosis	28	47	18–70	C. R. V. 18 64%

It is possible to speculate on both of these conditions regarding their relationship to the clinical condition of cardiorenal vascular disease. As will be seen both conditions are associated with this syndrome in 66 per cent of cases. Sampling at random two series of 100 consecutive autopsies we encountered cardiorenal vascular disease in an average of 50 per cent of the cases. Whether the high incidence of cardiorenal vascular disease associated with chronic adrenalitis or fibrosis, 66 per cent, is sufficient to be more than suggestive we are not prepared to state at the present time. Also, we could not demonstrate to our own satisfaction any difference when the cellular infiltration was cortical or medullary. Further study, however, is being made of the possible relationship to both of these conditions.

TABLE IV
TUBERCULOSIS OF ADRENALS
P. G. H. 1867-1932
Listed, 216. Studied, 55

Black	31	White	24
Males	47	Females	8
Addison's disease			2

An interesting sub-group of the inflammatory diseases of the adrenal is that of tuberculosis. Of these we had an opportunity to study 55 histologically. Table IV shows the sex and color distribution. Another interesting observation which is not revealed in the Table is that only 14 of the 216 cases showing active tuberculosis of the adrenals occurred since 1926, a reported incidence of .02 per cent. Prior to that time the incidence in 18,000 autopsies was 1 per cent.* Of the cases studied histologically only two were associated with the clinical evidence of Addison's disease, though nine additional cases were seen in the gross specimens.

*Deaths from Addison's disease in the United States have been practically constant, 0.4 per 100,000, for the last 15 years.

TABLE V

CLINICAL MANIFESTATIONS OF ADDISON'S DISEASE

1. Asthenia—fatigue.
2. Pigmentation—dermal, buccal, labial, black freckles.
3. Anorexia—nausea—vomiting.
4. Loss of weight.
5. Dizziness—syncopal attacks.
6. Arterial hypotension.
7. Dehydration—circulatory failure.

The majority of the symptoms listed in Table V were present in the clinical records of the cases before they were accepted as true Addison's disease. Of these eight were verified pathologically. In addition five cases were picked up at autopsy, unrecognized prior to death, showing tuberculosis of the adrenal glands, together with emaciation and bronzing of the skin or mucous membrane, and, a review of the clinical records showed that they were also true cases of Addison's disease clinically. From the standpoint of gross pathology, nine cases of Addisons' disease had tuberculosis of which only two were examined histologically. Two showed evidences of gross amyloid infiltration. One of these showed on histological examination a diffuse amyloidosis of most of the parenchymatous organs with lues as the etiological factor (Table VI).

TABLE VI

ADDISON'S DISEASE

P. G. H. 1867-1932

Clinically diagnosed	12	Pathologically proven	8
Not clinically giagnosed	5	Pathologically proven	5
Total	17	Total	13

PATHOLOGY

	Gross	Histologic
Tuberculosis	9	2
Atrophy	2	1
Amyloid	2	1 (luetic)

DEGENERATIVE DISEASES OF THE ADRENAL

Sections of only 45 adrenals exhibited pure degenerative processes. In 24 of these a parenchymatous degeneration was seen similar to the parenchymatous degeneration of other organs. They were most commonly associated with clinical conditions running an acute or subacute febrile course. Both cortex and medulla were affected. In many instances the medulla appeared "moth-eaten," suggesting the picture observed by Cramer experimentally in an actively secreting gland. In the medullas of certain adrenals we also found so-called "inclusion bodies" taking a pale eosin stain. These varied in size, were spherical in outline, and scattered throughout the chromaffin cells. No distinct correlation could be made between their incidence pathologically and the clinical condition of the patient. They were

most commonly present in cases of tuberculosis, bronchopneumonia and cardiorenal vascular disease. Incidentally they were also observed in many adrenals listed under other pathological headings.

TABLE VII

DEGENERATIVE DISEASES

P. G. H. 1867-1932
Listed, 184. Studied, 45

		Associated Diseases
Parenchymatous	24	Acute febrile 21 (T. B. 13 BPn. 8)
Medullary (inclusion bodies)	15	T. B. 10 C. R. V. 6 BPn. 4
Arteriosclerosis	6	6 C. R. V. 5

C. R. V.—Cardiorenal vascular disease.
BPn.—Bronchopneumonia.

Only six cases of pure arteriosclerosis were histologically verified in the entire series although scores were listed grossly, emphasizing again the lack of interest in the adrenal gland from the standpoint of general pathology.

TABLE VIII

DISTURBANCES IN LIPOID CONCENTRATION

P. G. H. 1867-1932
Listed, 109. Studied, 59

	Total	Associated Diseases	Age
Repletion	21	C. R. V. 14 Bronchopneumonia 11	40–70
Depletion	16	Cancer 6 Bronchopneumonia 6	40–60
Exhaustion	22	Acute febrile disease (Tuberculosis 11) (Bronchopneumonia 6)	20–40

DISTURBANCES OF LIPOID CONTENT

The amount of lipoid found histologically in this study of the adrenals varied somewhat with the clinical condition of the patient. In general, however, disease running a very acute or prolonged subacute febrile course associated with wasting and prostration, showed at autopsy almost complete exhaustion of the lipoid in the cortical cells of the adrenal. Lobar pneumonia and pulmonary tuberculosis are typical examples. On the other hand, cases dying an acute sudden death showed the cortex of the adrenal to be well filled with lipoid droplets. An intermediate phase of lipoid depletion as opposed to exhaustion is seen in conditions associated with wasting or only moderately prolonged febrile conditions, as, for instance, bronchopneumonia in elderly people, malignant disease, etc. The last portion of the cortex to lose its lipoid is that part of the zona fasciculata just beneath the zona glomerulosa.

TABLE IX

INFILTRATION

P. G. H. 1867-1932
Listed, 62. Studied, 26

ASSOCIATED DISEASES

Amyloid..... 22	Tuberculosis..... 15	Lues..... 5
Leukemia..... 2	Lymphoid..... 1	Myeloid..... 1
Hodgkins..... 2		

INFILTRATIONS OF THE ADRENAL GLAND

Nothing of extreme pathological or clinical interest was encountered in infiltration of the adrenal gland. Twenty-two cases showing amyloid infiltration were examined histologically. Of these, 15 were caused by tuberculosis; five by lues. In some instances the portion of the adrenal gland chosen for section showed the cortex to be infiltrated with amyloid to an estimated extent of 98 per cent. The clinical record of many of these cases was closely examined for evidences of Addison's disease but nothing suggestive was found, except in one instance.

Two cases of leukemic infiltration were found; one lymphatic, the other myeloid. Also, two cases of Hodgkin's disease showed the typical granulomatous infiltration into the adrenal with no clinical symptoms of Addison's disease.

TABLE X

P. G. H. 1867-1932
32 Listed. 13 Studied

TYPE OF LESION

Hemorrhage—	
Adults—Acute febrile diseases.....	7
Children—Symptoms of hemorrhage and shock.....	2
New born—Symptoms of hemorrhage and shock.....	2
Infarction—cardiorenal vascular disease.....	2
Total.....	13

HEMORRHAGE AND INFARCT

Thirty-two cases of hemorrhage or infarct of the adrenal gland were listed grossly in the autopsy protocols examined but only 13 were sectioned and could be studied histologically. Of these, seven occurred in adults presenting an acute febrile disease. Hemorrhage was not massive, although some of the cases clinically exhibited rather marked prostration. Rather massive hemorrhage was encountered in two children presenting symptoms of hemorrhage and shock. In neither of these cases was the diagnosis of hemorrhage into the adrenal suspected. Two cases of elderly individuals with myocardial failure showed small hemorrhages into the adre-

nals, probably the result of static infarction. The smaller hemorrhages seemed to arise at the junction of cortex and medulla. Information is desirable relative to the adrenal glands in all the various forms of purpura.

TABLE XI

HYPERTROPHY AND ATROPHY

P. G. H. 1867-1932

Hypertrophy of cortex	4	Malignant hypertension	2
Hypertrophy of medulla	9	General degenerative disease (Type not determined)	5
Atrophy of cortex	7	Addison's disease	1

HYPERTROPHY AND ATROPHY OF THE ADRENAL

Some difficulty was experienced in confirming the previous pathological diagnosis of hypertrophy or atrophy. It is to be remembered that all the sections examined were removed in a routine manner and in this review we had no absolute means of knowing from which portion of the adrenal these sections were removed. We used as a criterion for hypertrophy of the cortex or medulla both increase in size of individual cells or an increase in cells per unit area. In occasional instances we were able to see active mitotic figures. Four cases of hypertrophy of the cortex were encountered but in no instance were there any evidences of an increase in hormonal secretion as evidenced by hirsutism, virilism, etc. Two occurred in young individuals; two in old, the latter exhibiting an associated cardiorenal vascular syndrome. Six additional cases of microscopic nodular hyperplasia of the cortex were studied but these could not definitely be linked up with any clinical manifestations.

Nine cases of hypertrophy of the medulla were studied. Two of these occurred in individuals in their early twenties in whom a clinical diagnosis of malignant hypertension had been made. The remaining seven showed no evidences of intermittent or paroxysmal hypertension after close study of the original clinical record.

Seven cases of atrophy of the cortex were found whether primary or secondary, we do not know. In five of these there was an associated degenerative disease of a type undetermined but characterized by fibrosis and atrophy of most of the parenchymatous organs. These five cases occurred between the ages of 40 and 60 and were associated clinically with emaciation and weakness. Heart, liver, spleen, kidneys, pancreas, etc., were all well below normal weights and showed microscopically atrophy and fibrosis. One case exhibited a definite syndrome of Addison's disease.

The miscellaneous cases studied included a varix and localized calcification of the adrenals, the origin of which could not be determined pathologically. No case, however, showed any clinical symptoms referable to the adrenal gland.

TABLE XII

NEOPLASMS

P. G. H. 1867-1932
Listed, 202 (210?) Studied, 97

Primary		55
Metastatic		42
Gastrointestinal	16	
Breast	8	
Melanoma	4	
Epidermoid	3	
Lung	3	
Miscellaneous	8	

NEOPLASMS OF THE ADRENAL

Table XII shows the number and type of primary and metastatic tumors of the adrenal examined. It will be noted that 202 are listed, with a possible inclusion of eight more. This difference is accounted for by the description in many of the old protocols of yellowish spherical nodules attached to the periphery of the gland or located in the cortex. These were frequently diagnosed as miliary tubercles. In the absence of demonstrable tuberculous lesions elsewhere in the body, it was felt that these were probably small adenomata although no histological sections could be examined to confirm this opinion.

The metastatic tumors listed exhibited great variety in type of tumor and point of origin. In the sections showing early metastatic lesions the focus in the adrenal seemed to originate in the region between cortex and medulla, infiltrating more readily into the medulla, but in some instances spreading into the cortex. Regardless of the amount of adrenal tissue destroyed, no case exhibited clinical signs of adrenal insufficiency.

TABLE XIII

PRIMARY TUMORS

P. G. H. 1867-1932
Listed, 116 (124?) Studied, 56

Adenomas	33
Cortical Tumors— (Adenocarcinomas 2, Hypernephromas 4, Mixtures 2)	8
Medullary Tumors— (Neuromas 2, Angioblastoma 1, Sympathicoblastoma? 7, Glioblastoma? 4)	14
Cyst	1

The primary tumors are subdivided in Table XIII with respect to their types. Thirty-three benign adenomas were studied histologically. These varied from small collections of cortical cells just outside the capsule of the gland, 3 mm. in diameter, to benign tumors several centimeters in size. Examination of the smaller adenomas in some instances shows the cortex

of the adrenal herniating through the capsule of the gland to form the small extra-capsular adenomas. This suggests that at least in some instances the adenomas may be of post natal origin rather than congenital. In no instance was medullary tissue found in any adenoma. The histology of these adenomas varied from cells comparable in size to those in the normal cortex of the gland to large pale staining cells filled with lipoid material. As a general rule no uniform architecture was maintained in these benign tumors unless the adenoma was attached to the gland proper. In such an instance it usually bore, at least in the cases studied, more resemblance to the zona fasciculata than to the zona glomerulosa. In the smaller adenoma attached to the gland the lipoid present in the tumor was affected by the general clinical condition of the patient just as was the lipoid content of the cortex of the normal or diseased gland.

TABLE XIV

ADRENAL ADENOMAS

P. G. H. 1867-1932
Listed, 66. Studied, 33

AVERAGE AGE, 64

Sex		Color		Associated Diseases	
Male	16	White	24	C. V. R.	28
Female	17	Black	9	Carcinoma	10
				Bronchopneumonia	18

The average age of the cases studied, the color and sex distribution are shown in Table XIV. In no instance could disturbances in sex characteristics be determined after careful perusal of the clinical record nor was a cortical adenoma of the adrenal suspected or diagnosed clinically in any case. There is no record in the 25,000 autopsies of a single case of a so-called secreting adenoma. In one instance, pseudohermaphroditism in a negress, 49 years old, was found in which the clitoris was enlarged to 5 by 1 cm. but the adrenals were normal. In our surgical file there is only one case of secreting adenoma. This specimen was removed at operation in the region of the left kidney in a four-year-old girl, who presented a heavy growth of pubic hair, rather coarse heavy features and an extremely deep voice for a child of her age. The patient died a few days after removal of the tumor but post mortem examination was denied. Exploration through the operative incision, however, revealed an absence of the adrenal on the left side with a normal adrenal by palpation on the right.

The primary tumors of the adrenal, apart from the cortical adenomas, have been of extreme interest but have presented the greatest difficulty from the standpoint of diagnosis. When one considers the complicated embryological development of the adrenals one can realize quite readily the potentiality relative to tumors. In the present review we have divided the group into those of cortical and those of medullary origin.

CORTICAL TUMORS OTHER THAN ADENOMAS

These were eight in number; two rather typical adenocarcinomas. One occurred in a white male aged 66 and was present in both adrenals. It had not metastasized. The other occurred in a white female aged 50. Both adrenals were involved and there had been metastasis to the liver, right lung and pleura, and right orbit. The diagnosis was concurred in by several competent pathologists on the staff of the hospital. No special clinical picture developed in these cases.

There were four cases of hypernephroma. Although three cases showed metastatic nodules in one kidney, the size of the tumor in the adrenal made us believe it to be the primary site. In two cases only was the other adrenal involved. No case showed any disturbance of secondary sex characteristics. There are on file 22 cases of hypernephroma probably renal in origin. These will be examined in detail and reported subsequently.

There were two cases which presented peculiar pathological lesions of primary adrenal origin which for want of a better term we have designated as "mixtures." Both of these occurred in elderly individuals, had widespread metastases with a decided difference in the histological picture between the primary tumors in the adrenal and the metastatic lesions. Both were thought to be of cortical origin but no concurrence in type of tumor was possible from the report received from various pathologists attached to the hospital. The secondary metastatic nodules resembled hypernephroma histologically. No clinical picture was presented.

MEDULLARY TUMORS

In the total series of primary tumors we encountered 13 of the medullary origin. These presented the greatest difficulty in diagnosis from the standpoint of cell origin and type of tumor. We must emphasize again that this review has been made on sections cut in a routine manner and stained with simple hematoxylin and eosin. For this reason we are not prepared to state positively that the diagnoses made are final. At the present time we are concerned with re-cutting the old paraffin blocks and studying sections stained by special neuropathological methods in conjunction with Dr. N. W. Winkelman of the Division of Neuropathology. A more detailed report will be submitted later. For the present we have been content to divide the medullary tumors into two sub-groups: those of neurogenic or sympathicoblastic origin and those of glial or glioblastic origin.

In the former group we have studied seven. All these occurred in patients over 29, with one exception. Only one case showed absence of metastases. This occurred in a black female aged 66. This tumor was small, circumscribed, located in the central portion of the right adrenal. On section it showed the typical rosettes of neurocytoma. None of the other tumors in this group presented the typical clinical picture as described by Hutchinson or by Pepper, although two showed metastases to brain and skull, and two to lung and liver. The previous diagnosis on two

of these cases had been primary carcinoma probably of medullary origin and one had been diagnosed as a retroperitoneal sarcoma. This latter case showed involvement of both adrenals. The exception noted occurred in a little girl three years of age presenting a large retroperitoneal tumor mass with metastases to liver, lung, skull and brain. The clinical diagnosis was that of retroperitoneal sarcoma although the picture was fairly typical of Hutchinson's type of adrenal tumor. The pathological diagnosis was sympathicoblastoma.

Four tumors were diagnosed paraganglioma (spongioblastoma?). These occurred in individuals of less than 50 years. One only showed absence of metastases. There was nothing indicative of paroxysmal intermittent hypertension in any case studied.

Two cases of simple neuroma were encountered, localized to the medullary region of the adrenal and one case of angioblastoma with metastasis to the lungs.

ABNORMALITIES

Three cases were noted in the 5,000 post mortems prior to 1900, in which no adrenals could be found. Two supernumerary adrenals are recorded in the same period. No microscopic sections were available on these supernumerary adrenals and it is possible that they may be simple discrete adenomas. Only one malposition of the adrenal was noted, in which it overlay the convex lateral surface and not the upper pole of the kidney.

DISCUSSION

In this preliminary survey of 25,000 autopsies it is astounding that 511 adrenals only were considered of sufficient interest to warrant histological examination. This indicates a lack of interest on the part of both clinicians and pathologists in the physiology as well as in the pathology of the adrenal gland. It would suggest that greater attention should be paid to these organs in order to understand more thoroughly their relationship to the bodily constitution as a whole and the other endocrine glands in particular. This preliminary study suggests several leads for further work. What types of cells are present; what is their origin, their function and their hormonal influence? Is the relationship which we have observed between chronic adrenalitis and disease of the cardiorenal vascular system, real or only apparent? Does the atrophy of the cortex of the adrenal bear any relationship to the atrophic and degenerative condition of the parenchymatous organs which we observed? Are the so-called secreting adenomas of the adrenal which produce such appalling changes in the sexual development of patients of adrenal origin, solely, or may these so-called secreting adenomas of the adrenal originate from some of the primitive undifferentiated sex cells which have remained behind in the region of the adrenal (or kidney) during the descent of the testicle or ovary? Are the sympathicoblastomas (neurocytomas) with visceral or skeletal metastases

distinct clinical entities as described by Pepper and Hutchinson or are they sub-groups of the same primary cell, metastasizing by different routes? Are the so-called paraganglioma entirely responsible for the associated permanent or intermittent hypertension? With the apparent lack of concurrence among competent pathologists in diagnosing tumors of medullary origin, there is great need of further investigation to determine whether the cells are of neuroblastic, glioblastic or sympathicoblastic origin. These are but a few of the suggestions for further study gained by this survey. If we have been successful in revealing the lack of interest heretofore exhibited in the pathology of the adrenal and the need for further information and have thereby stimulated the interest of some pathologists and some clinicians in the relationship between general disease and the pathology of the adrenal, the time spent in reviewing these 25,000 post mortems will, in our opinion, have been worth the effort.

SUMMARY

A consecutive series of 25,000 autopsies was reviewed to determine the incidence and types of adrenal disease and its relation to general and special bodily states. Beyond a surprising lack of interest in the adrenals, as evidenced by mention of pathologic changes in only 925 instances, nothing noteworthy or definitely new came of the survey. In a limited number of cases, however, suggestive relationships were observed between chronic adrenalitis and cardiorenal vascular disease and cortical atrophy associated with atrophy of the parenchymatous organs. The need for further investigation of tumors of the adrenal is indicated to determine the cells of origin not only in those arising in the medulla but also in those cortical adenomas causing such marked changes in sexual characteristics.

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Book Review

PATHOLOGIE UND PATHOLOGISCHE MORPHOLOGIE DER HYPOPHYSE DES MENSCHEN. Walter Berblinger. Separate publication from Band I, "Handbuch der inneren Sekretion." P. 187. Ed. M. Hirsch, Berlin. 1932.

Berblinger brings up to date the German literature on the pathology of the hypophysis and reviews the more outstanding literature in other languages.

The volume comprises two sections—a study of the changes in the hypophysis in relation to various clinical conditions and of the pathological anatomy of pituitary diseases. In the first section the conditions dealt with are pregnancy, castration, thyroid diseases, parathyroid deficiency, adrenal and pancreas deficiency, neoplasms and renal disease. The second section is introduced by a sketchy discussion of the pituitary hormones, citing 12 German and two French articles. The pituitary disorders that are discussed are Simmonds' disease, dwarfism, hypophyseal infantilism, acromicria, dystrophia adiposo-genitalis, diabetes insipidus, gigantism, acromegaly and primary pituitary tumors.

The monograph is most significant as an exposition of Berblinger's own voluminous work in a field in which he is a well-known authority. He takes issue with recent work that indicates that the pars intermedia is an important entity. The volume is almost profusely illustrated from well-selected original material. The text is clear and well-organized. The format is in keeping with the general excellence of the book.

Abstract Department

Lactic acid formation during muscular work after removal of the suprarenal glands (Die Milchsäurebildung be Muskelarbeit nach Entfernung der Nebennieren). von Arnay, A. and L. Lengyel, Biochem. Ztschr. **239:** 128. 1931. Abst., Physiol. Absts. **17:** 440.

The formation of lactic acid in 67 muscles taken from adrenalectomized rats during rest, work, after tetanic stimulation, and in rigor was found to be very greatly diminished.

Treatment of Addison's disease with cortin (Hartman); report of four cases. Baird, P. C. and F. Albright, Arch. Int. Med. **50:** 394. 1932.

Four patients with Addison's disease have been treated with cortin (Hartman's extract). Of these, three were in all likelihood suffering from tuberculosis of the suprarenal glands and one from primary atrophy of the suprarenal cortex. We believe that all the patients received benefit from treatment. A scientific evaluation of the efficacy of treatment is curtailed by the absence of a chemical or physical variable that fluctuates proportionately to the degree of suprarenal insufficiency, and that can be accurately measured. The clinical evaluation of the efficacy of treatment rests chiefly on the following factors: (a) disappearance of nausea and vomiting, (b) restoration of appetite, (c) increase in strength and feeling of well-being and (d) prevention of death in acute suprarenal insufficiency (this is the most important). In one patient with acute suprarenal insufficiency in a moribund condition, the administration of cortin alone, without any adjuncts to treatment, produced a dramatic result. The nonprotein nitrogen of the blood was reduced to normal, and the blood sugar was elevated to normal, concomitant with treatment. The effect of cortin on ergographic tracings, blood pressure, pigmentation, blood cholesterol, blood nonprotein nitrogen, blood creatinine, blood sugar, urinary excretion of creatine and creatinine, the basal metabolic rates and electrocardiographic tracings have been studied and discussed. None of these possible variables has been found of value in the following of the fluctuations in the degree of suprarenal insufficiency. The tendency to subnormal temperature was decreased by treatment with cortin. It was further noted that three acute episodes of suprarenal insufficiency were ushered in by subnormal temperatures. The subnormal temperatures may have been the cause or the result of the insufficiency. Cortin has proved of the most value in the treatment of patients who are in a prostrate and moribund condition. Thus in the clinic as in the laboratory the best measuring stick of its efficacy remains the test of life or death.

—Authors' Summary.

Adrenogenital syndrome associated with cortical hyperplasia: results of unilateral adrenalectomy. Broster, L. R. and H. G. Hill, Brit. J. Surg. **19:** 557. 1932. Abst., J. A. M. A. **99:** 346.

Broster and Hill performed unilateral suprarenalectomy in three cases representing three different types of the suprarenogenital syndrome associated with suprarenal cortical hyperplasia—namely, pseudohermaphroditism, virilism or hirsutism, and the Achard-Thiers syndrome (diabetes of fat-bearded women). All three patients made complete recoveries and are in good health. In no instance were untoward postoperative symptoms observed, and the blood pressure did not vary during or after operation. The effects of unilateral suprarenalectomy on the main symptoms of the syndrome, the hypertrichosis, and sex changes were not the same in the three cases. In the late syndrome (suprarenal virilism) markedly beneficial results were obtained, but in the early form (pseudohermaphroditism) and in the Achard-Thiers type (probably a pluriglandular disturbance) no change in the symptoms was observed. The authors' experience would therefore suggest that unilateral suprarenalectomy is indicated in the late syndrome (virilism) due to suprarenal cortical hyperplasia, when the suprarenal lesion is mainly unilateral, but not in the other two forms.

Method for a biologic estimation of the adrenal cortical extract (Methode pour le dosage biologique de l'extrait de corticale surrénale). De Meio, R. H. and J. T. Lewis, Compt. rend. Soc. de biol. **111:** 822. 1932.

Five rats from 150 to 200 grams are used for each test. On the 4 days immediately following double adrenalectomy, they receive doses of extract subcutaneously. Five or six days after the last dose a subcutaneous injection of 8 mg. of morphine hydrocloride per 100 grams body weight is given. A rat unit is the least amount of cortical extract which will preserve all of the five rats in a group from the lethal action of the morphine. Examples of several tests of extracts are given. With non-toxic extracts, doses representing 20 to 30 grams of the original adrenal gland per 100 grams of rat were effective.

—J. C. D.

The influence of the adrenal on the metamorphosis of Amphibians (Über den Einfluss der Nebenniere auf die Metamorphose bei Amphibien). Eskin, J. A., Endokrinologie, **11:** 249. 1932.

After studying 31 experimental and 15 control Axolotl the author concludes that feeding 0.05-0.025 gm. of fresh cortex of the adrenal by mouth every other day results in a definite acceleration of metamorphosis (first noticed about the sixth day), while feeding or implantation of medulla of the adrenal, heart muscle or skeletal muscle is without effect on the metamorphosis. Implanting 0.01 gm. of cortex of the adrenal in the body also hastened metamorphosis. The thyroid gland is observed to undergo a change which consists in a transformation of the epithelium to a cuboidal or columnar type and a fading and vacuolization of the colloid filling the alveoli.—R. A. Phillips.

Traumatic shock in adrenalectomized rats. Freed, S. C., Proc. Soc. Exper. Biol. & Med. **30:** 677. 1933.

Adrenalectomized, but not normal, rats are sensitive to trauma and usually die from moderate tissue injury. Injection of normal saline is effective in protecting shocked rats from death. The toxemia theory of shock explains this susceptibility of adrenalectomized rats to injury.—Author's Summary.

Temperature regulation and the suprarenals. Morphologic study of the activity of the medulla of the suprarenal (Surrénales et thermorégulation. Tests morphologiques d'activité médullo-surrénale). Goormaghtigh, N., Arch. di biol. **41:** 109. 1931. Abst., Chem. Absts. **26:** 3560.

The adrenaline content of the suprarenal medulla of mice, as determined by morphologic methods, appears to be decreased when the body temperature is lowered 2°. The content remains normal or is increased when the temperature is increased. After a moderate loss of heat from the body, the "osmophile reaction" is increased: after a marked loss, the reaction is diminished.

Observations on the hormone of the adrenal cortex. Grollman, A. and W. M. Firor, Am. J. Physiol. **101:** 46. 1932.

Swingle and Pfiffner's method of preparation of the cortical hormone of the adrenal may be appreciably shortened and improved by extracting the glands with acetone, instead of alcohol. After removing the solvent and extracting with benzene, epinephrine is removed by dilute alkali. This simplified process yields a product free of the toxin which is often present in the extracts prepared by Swingle and Pfiffner's or by Hartman's method. This toxin is an indolephenolic derivative probably identical with the "omega" substance formed on exposing epinephrine to sunlight. It is cherry-red in color, turning brownish-black on standing and may be separated by extracting the active principle with ether. The use of colored extracts is to be avoided particularly in clinical cases. Suspected solutions may be tested by injecting one cubic centimeter into a mouse, death ensuing in a few minutes to an hour, depending on the amount of the toxin present. The most satisfactory test animal for determining the potency of the extract is the rat. Removal of the veil of connective tissue surrounding the adrenal bodies and avoidance of crushing of the glands resulted, in our series of over 100 animals, in death usually within 1 to 12 days after operation or cessation of the extract. The pre-operative treatment of animals is an important factor in determining their survival period after adrenalectomy. Cats subjected to cold for several days before operation show the cardinal signs

of adrenal insufficiency (loss of weight, tendency to infection, and lack of resistance to cold) and may die (particularly young animals) even after unilateral adrenalectomy. This importance of pre-operative treatment accounts for the frequently observed apparent greater prolongation of life after two-stage operations as compared to the one-stage removal. We have found that the average amount of extract necessary to keep animals in good condition after adrenalectomy is greater than that claimed in the literature.—Authors' Abst.

Experimental erythropoiesis in the adrenal of splenectomized guinea pigs (Sur l'érythropoïèse surrénale expérimentale chez le Cobaye splénectomisé). Hayaski, K., Compt. rend. Soc. de biol. **111**: 712. 1932.

In splenectomized guinea pigs injected with phenylhydrazine hydrochloride evidence of formation of red blood cells in the areas around the capillaries of the zona reticularis was seen. The parenchyma cells were in direct contact with the new-formed cells.—J. C. D.

Case of Addison's disease treated with Swingle and Pfiffner's extract of suprarenal cortex. Holten, C. and E. Schidt, Ugesk. f. laeger **94**: 787. 1932. Abst., J. A. M. A. **99**: 1460.

The authors report the case of a woman, aged 40, with Addison's disease of probably twenty years' standing. A comatose condition had set in and the patient was almost moribund, when treatment with extract of suprarenal cortex, prepared according to the method of Swingle and Pfiffner, was begun. The effect was excellent and the patient is now almost able to work. The action of the preparation on the various symptoms and the dosage are discussed; a decline in the patient's psychic state is emphasized as the earliest and surest sign of underdosage.

The chromaffine and interrenal system of man (Das chromaffine und interrenale System des Menschen). Iwanow, G., Ergebn. d. Anat. u. Entwcklgsgesch. **29**: 87. 1932.

An extensive review of the phylogenetic and ontogenetic history of the chromaffine system, together with adult topographical relations, blood supply, innervation and structure. There is a consideration of the functional significance of its various components. Anomalies and pathology (including tumors) are briefly discussed. Nothing essentially new. Extensive bibliography to 1930. —A. T. R.

Quantitative studies on the cortex and medulla of the suprarenal gland in the adult guinea-pig (Quantitative Forschung von Nebennierenmark und-rinde beim erwachsenen Meerschweinchen). Kosaka, Y., Folia anat. japon. **10**: 601. 1932.

Examining the suprarenal glands of 16 adult guinea-pigs by means of the paper-weighing method, the author obtained the following results: 1. The weight of the gland, which is not always proportional to that of the body, averages 0.335 gram, and is 0.0734% of the body weight. Its specific weight is 1.0457. It is heavier in the female than in the male. 2. The left gland is always larger than the right, being heavier by 14.8%. 3. The volume of the medulla is not always proportional to either that of the gland or to body weight. Compared with the variation in the volume of the gland and that of the cortex, the individual variation in the volume of the medulla is very small. The medulla is 0.00531 cc., and its average weight is 0.00118% of the body weight. 4. The volume of the medulla does not differ greatly in males and females. 5. The volume of the cortex is proportional to that of the gland, the left cortex always being larger than the right. The volume of the cortex is on an average 96.5% that of the gland.—Author's Abst.

The influence of adrenalectomy on the fat content of different organs and the influence of sulfur on the fat content of adrenalectomized animals (Ueber den Einfluss der Epinephrektomie auf den Fettgehalt verschiedener Organe, insbesondere über den Einfluss des Schwefels auf disen Fettgehalt der epinephrektomierten Tiere). Kubo, S., Folia endocrinol. japon. **7**: 11. 1932. Abst., Chem. Absts. **26**: 5331.

After total adrenalectomy the increase in body weight of white rats was less than that of the controls and the fat content of the heart, liver, kidneys

and skeletal muscles tended to decrease. When adrenalectomized animals were fed sulfur the body weight increased more rapidly than in the adrenalectomized controls and the decrease in the fat content of the different organs was stopped.

Chemistry of the adrenals of mammals. Comparative study of the medulla and the cortex (Recherches chimiques sur les capsules surrénales des mammifères. Etude comparée de la zone médullaire et de la zone corticale). Leulier, A. and L. Revol, Bull. Soc. chim. biol. **13**: 211. 1931. Abst., Chem. Absts. **26**: 2225.

After extraction of the fresh tissue for ½ hour, the adrenaline content is determined by Bailly's method. In the sheep, goat, ox, calf, pig and horse very little, if any, adrenaline is found in the cortex, while the medulla contains considerable quantities of both free and "virtual" adrenaline, which vary from individual to individual in the same species. The "virtual" adrenaline is set free on keeping the tissue over sulfuric acid in a vacuum for 24 hours. The amount of free cholesterol varies within narrow limits, whereas the combined cortex contains rather more lipin and less total phosphorus than the medulla. Potassium is distributed equally in the organ, while the cortex contains the larger amount of total sulfur. Except for the horse, the cortex appears to be richer in nitrogen and to contain rather less water than the medulla.

Temperature studies in normal and suprarenalectomized rats. Martin, S. J. and F. Maresh, Am. J. Physiol. **101**: 74. 1932.

Temperature measurements were made with a thermo-couple which was inserted at least 5 to 6 cm. into the colon of adult rats. The colonic temperature observed on 335 normal female rats showed a most probable temperature of 38.2° C. with 50% of all determinations lying in the range 37.8°-38.6° C.; the most probable temperature of 193 male rats was slightly lower. The temperature distribution was the same for variations in weight, age, season and time of day. The vaginal temperature closely followed the fluctuations of the colonic temperature and was always about 1° C. below it. No correlation could be established between the vaginal temperature and the different stages of oestrum. The colonic temperature of completely suprarenalectomized rats remained normal until 24 to 72 hours after death; in the terminal stages, it declined rapidly. In all control animals the temperature was normal indefinitely. Control rats were subjected to a ten-minute period of ether anesthesia. The colonic temperature, taken before, during and after the procedure, showed a recovery to normal in about 2 hours in all cases. Experimental rats were similarly treated on different days after the second suprarenal was removed. It was found that (1) some rats failed to recover, (2) others showed an attempted recovery and subsequently died and (3) another group showed a normal or delayed recovery. No rats survived etherization after the tenth to twelfth day following complete suprarenalectomy. The body weight and colonic temperature were maintained beyond the survival period in some completely suprarenalectomized rats injected with the Swingle-Pfiffner hormone. In one case such an injected animal showed a typical normal recovery when given the ether rausch. The animal died in a few days when daily injections were stopped.—Authors' Abst.

Experimental investigation of the action of adrenaline and the destruction of the same in bodies of normal, starved and phosphorus-poisoned rabbits with special regard to the adrenaline poisoning by disturbance of liver function (Experimentelle Untersuchungen über die Wirkung des Adrenalins und die Zerstörung desselben im Körper bei normalen, phosphorvergifteten und hungernden Kaninchen mit besonderer Berücksichtigung der Adrenalinentgiftung bei Störung der Leberfunktion). Marui, E. and H. Machii, Folia pharmacol. japon. (Brev.), **13**: 24. 1932. Abst., Chem. Absts. **26**: 3843.

The action of adrenaline on blood pressure was followed in normal, starved and phosphorus-poisoned rabbits. The minimum dose to increase blood pressure was determined by injection through the ear and the mesenterial veins. Starved animals and those poisoned with phosphorus showed greater sensitivity to adrenaline than normals. Injection through the ear vein showed greater effect and the effect is greater in normals than in starved, and is least in those poisoned with phosphorus. After injection into the ear vein the adrenaline content of the blood was higher and continued longer than after injection into the mesenterial. There is much less destruction of adrenaline in the starved and poisoned animals.

Specificity of hypoglycemia hormone of suprarenal gland. Medvedeva, N. B., Jurnal Medichnogo Tsiklu, **2**: 479. 1932. Abst., J. A. M. A. **100**: 628.

Medvedeva, in a series of previously reported experiments, demonstrated that the suprarenal cortex contained a substance which, when injected subcutaneously, exhibited a distinct hypoglycemic effect. The maximum effect was noted from two and a half to three and a half hours after the injection. The blood sugar diminished until only traces were left, in some cases to the point of total disappearance from the blood. The action of the hormone did not apparently depend on insulin, since it was effective in diabetic dogs as well. To determine the specificity of the hormone, to which the author wishes to apply the name, "corticaline," the effect of various other tissue extracts were tried. Extracts were prepared by the same method from muscles, lungs, liver, pancreas, intestine, stomach and lymph nodes. Blood sugar determinations were made every half hour for four hours. None of the organs mentioned proved to possess an active principle capable of reducing the blood sugar. Muscle extracts were demonstrated to possess a distinctive hyperglycemic effect. These results support the author's belief in the specificity of corticaline as an active hypoglycemic hormone of the suprarenal cortex.

Use of cortin in a case of acute hyposuprarenalism occurring as a sequela of acute streptococcic sore throat. Robbins, J. H., J. A. M. A. **100**: 659. 1933.

A case of acute hyposuprarenalism occurred as a complication of acute streptococcic sore throat. The results of treatment with cortin in this case were very unsatisfactory. It is suggested that acute hyposuprarenalism may occur more often than is usually believed. If chronic hyposuprarenalism is a definite entity, cortical extract may prove of extreme value in combating its distressing symptoms.—Author's Summary.

The action of adrenalin upon the cardiac vagus centers. Stella, G., J. Physiol. **77**: 68. 1932.

It was found that intravenous injection of adrenaline that causes increased arterial pressure and bradycardia in dogs does not directly excite the cardioinhibitory centers but seems to sensitize them to afferent depressor and carotid sinus impulses. The bradycardia is a reflex effect from these regions. Although the number of experiments is not stated nor the consistency of results, apparently a large number of animals was employed.—C. I. R.

The adrenal-genital syndrome (Le syndrome surreno-genital de Cook-Apert-Gallais). Schereschewsky, N. A., Rev. franç. d'endocrinol. **9**: 104. 1931.

Report of a case with more or less typical symptoms which the author explains on neuro-pluriglandular basis rather than adrenal. The endocrine involvement is secondary.—B. C.

Function of the adrenal medulla. Svirbely, J. L. and A. Szent-Györgyi, Nature, **129**: 541. 1932. Abst., Chem. Absts. **26**: 4843.

Adrenaline appears to be a decomposition product of the substance primarily produced by the adrenal gland. When postmortem enzymic reactions are minimized by rapid excision and cooling of the glands, careful extraction with 0.5% trichlor-acetic acid gives a new substance, called "novadrenaline," which has a physiologic action different from that of adrenaline. For large doses the rise in blood pressure produced is higher than that produced by corresponding amounts of adrenaline. Novadrenaline appears to be an ester of adrenaline with the esterifying radical attached to the side chain.

Hexuronic acid as the antiscorbutic factor. Szent-Györgyi, A., Nature, **129**: 943. 1932. Abst., Chem. Absts. **26**: 5128.

This is a brief comment on the experiments described by Zilva, abstracted in this number. These experiments confirm Szent-Györgyi's opinion that hexuronic acid is the antiscorbutic factor.

Influence of adrenine on the blood pressure curve in asphyxia (Effet de l'adrénaline sur le tracé de la pression sanguine pendant l'asphyxie). Walawski, J., Compt. rend. Soc. de biol. **111**: 95. 1932.

Cats (number not given) were used. Some cats were intact, others had the spinal cord cut below the bulb, the cord entirely destroyed, the splanchnics cut, or the adrenals removed. The rise of blood pressure during asphyxia shows three consecutive steps. The first of these is due to the direct action of CO_2 on the nerve centers, and the second to the release of adrenine in response to nervous stimulation. The third or terminal phase is the result of a direct secretion of adrenaline without intervention of the nervous system.—J. C. D.

The significance of natural variations in the structure and cortical lipoid of the mouse suprarenal. Whitehead, R., Brit. J. Exper. Biol. **12**: 305. 1931. Abst., Physiol. Absts. **17**: 528.

Suprarenals were studied from 65 healthy mice of different ages and sexes and from 20 mice in which the suprarenals were stimulated by exposure to cold and wet or by adrenaline injections. The results confirm those of Miller on the structure and involution of the X zone, but do not support Cramer's impression that when the medulla has been stimulated there is a centripetal movement of lipoid. Lipoid is relatively more abundant in the suprarenal cortex of female than of male mice aged about 150 days. The changes seen after stimulation of the gland were activity of the medulla and sometimes a decrease in cortical lipoid. The recognition of natural sex differences in the mouse suprarenal removes the histological basis for Cramer's theory of self-control. Cramer's interpretations cannot be accepted, since they were made on the assumption that natural variations do not occur in the mouse suprarenal.

Hexuronic acid as the antiscorbutic factor. Zilva, S. S., Nature, **129**: 943. 1932. Abst., Chem. Absts. **26**: 5128.

Experiments are described that show the presence of the antiscorbutic factor in the preparation used, but do not prove the identity of hexuronic acid with the antiscorbutic factor.

Endocrine glands in cirrhosis of liver (Les glandes à sécrétion interne dans la cirrhose hépatique). Barrelet, J., Ann. d'anat. path. **9**: 385. 1932. Abst., J. A. M. A. **99**: 348.

The author reports the results of a systematic anatomic and histologic postmortem study of the glands of internal secretion in persons with cirrhosis of the liver. In the majority of cases of cirrhosis the endocrine glands exhibited modifications in their anatomic and histologic structure. The testes in a majority of the cases revealed atrophic lesions of the seminiferous tubules, accompanied in about half the cases by increase of the interstitial cells. In cases of Laënnec's cirrhosis, atrophy of the testes was constant and more advanced in the atrophic stage than in the hypertrophic stage, in which the testes may present a normal structure. These lesions occur independent of age and intercurrent diseases. Fibrosis of the testes was found in only one case. In young women with cirrhosis, fibrous ovaries without germinal follicles were found only once. The thyroid presented atrophic changes in the form of loss of weight and a degeneration of the colloid, whose structure was modified. The colloid was often basophilic and in 79% of the cases exhibited vacuoles filled with fine granulations, refractive and mucoid in character. The hypophysis sometimes showed an increase of basophilic cells at the expense of eosinophilic cells; almost equally often the chromophobic cells were increased in number. Basophilic elements were never found in the posterior lobe of the hypophysis. The suprarenals were deficient in lipoids in about half the cases of cirrhosis; the cortex sometimes revealed an increase of the connective tissue and the pseudoglandular lumens. In half the cases the pancreas showed proliferation of the connective tissue, followed by atrophy of the glandular parenchyma. In 6% of the cases the fibrosis extended to the islands of Langerhans and had clinically given rise to diabetes. In 25% of the cases the pancreas appeared unaltered.

Chemical and biological investigation of the effective principle of lymph-node extract (Ricerche chimiche e biologiche sopra i principi attivi degli estratti di gangli linfatici). Christoni, A., Rassegna di terap. e pat. clin. **2:** 65. 1930. Abst., Chem. Absts. **26:** 5137.

Aqueous lymph-node extract exerts an action antagonistic to adrenaline; the active principle is precipitated by alcohol but not by phosphotungstic or phosphomolybdic acids. It is highly probable that it is not a choline but an amino acid derivative of hormone-like action.

The influence of some organ extracts on the permeability to water of sea-urchin eggs (Arbacia punctulata). Favilli, G., J. Cell. & Comp. Physiol. **2:** 1. 1932.

Mammalian testicle extract and spleen extract has been studied in their effect on the permeability of cells to water. The unfertilized egg of the sea urchin, Arbacia punctulata, was employed as a natural osmometer with which to measure changes in permeability. It was found that extracts of these organs distinctly increase permeability to water in concentration of 1:100 and still distinctly but to less extent in concentration of 1:400. Blood serum has slight power to increase permeability. Several proteins were found inactive in this respect. It has previously been reported that testicle extract increases fragility of mammalian erythrocytes. The relation of the present experiments to those on erythrocytes is discussed. It is believed to be significant that these organ extracts increase permeability even in the presence of normal concentrations of Ca and Mg, substances which ordinarily stabilize the permeability of the cell.
—Author's Abst.

Auxoneurotropic action of epinephrine and of solution of pituitary (Über auxoneurotrope Wirkung des Adrenalin und Hypophysin). Friedemann, U. and A. Elkeles, Deutsche med. Wchnschr. **58:** 423. 1932. Abst., J. A. M. A. **99:** 789.

In animal experiments for production of anesthesia by artificial perfusion of the brain, the authors found that intravenous injection of epinephrine and of solution of pituitary reduced the threshold value of anesthetics such as ethyl urethane, paraldehyde and alcohol to about one-fifth; that is, one-fifth of the usual anesthetic dose was sufficient to produce anesthesia. Other hormones, such as insulin and thyroxine, did not have this effect. It was also noted that the toxic action of strychnine and of cobra toxin was increased five-fold by epinephrine and solution of pituitary. By special methods of staining it could be demonstrated that the auxoneurotropic action of epinephrine and solution of pituitary can be traced to an increased invasion of neurotropic substance into the brain. Substances that are not neurotropic, such as arsphenamine, antitoxin and trypan blue, do not enter the brain even under the influence of epinephrine or solution of pituitary. The authors discuss the significance of these observations for pharmacologic, chemotherapeutic, serotherapeutic and pathogenic problems.

Method of recording and interpreting results derived from the sero-interferometer method of Hirsch applied to endocrine dystrophies (Mode d'expression et interprétation des résultats fournis par l'examen séro-interférométrique de Hirsch dans l'etude des dysendocrinies). Guillaumin, C. O., Compt. rend. Soc. de biol. **110:** 1295. 1932.

The method is based on Abderhalden's theory of defensive ferments and is supposed to measure cell destruction. Hirsch combines the serum from a patient with equal parts of material from a normal gland of the kind to be tested under proper conditions. After 24 hours, the serum is separated in a centrifuge and its fermentative activity determined by the increased molecular concentration as measured by the interferometer. Results must be expressed as percentages of the original fermentative activity and not simply as interferometer readings. Increased values in the serum indicate reduced activity of the patient's gland; reduced values an increased activity. Studies were made on 550 patients. No details are given.—J. C. D.

Functions of the grafted gall bladder. Duodenal cholecystokinetic hormone (La función de la vesícula biliar injertada y la hormona duodeno-colecistoquinética). Houssay, B. A. and H. H. Rubio, Rev. Soc. argent. de biol. **8**: 369. 1932.

A method is described which permits the grafting of the gall bladder by anastomosis of the celiac trunk with the carotid and a portal vein with the external jugular. The contractions of the gall bladder are registered. Warmed at 38°-39° C. the graft survives in excellent condition for several hours at least. Acid introduced into the duodenum increased the tone and contractions of the grafted gall bladder in 7 of 11 experiments. Cream and egg-yolk introduced in the duodenum had no kinetic effect on the grafted gall-bladder, but bile was excreted into the gut (3 experiments). Cholecystokinin prepared according to Ivy's technique when injected intravenously had a kinetic effect on the grafted gall bladder.—J. T. L.

Correlation of the five hormone organs: hypophysis, thyroid, thymus, testes and suprarenal, in normal man and domestic animals, by means of the interferometric method of the Abderhalden reaction (Über die korrelativen Verhältnisse der 5 Hormonorgane Hypophyse, Schilddrüse, Thymus, Keimdrüse und Nebenniere bei gesunden Menschen und Haustieren auf Grund experimenteller Untersuchungen mittels der interferometrischen Methode der Abderhaldenschen Reaktion). Lendel, E. and F. Hogreve, Fermentforsch. **13**: 244. 1932. Abst., Chem. Absts **26**: 4088.

In domestic animals (horses and cattle) and in man there is an intimate relationship between thyroid and reproductive glands, but essential differences are found in the correlation between hypophysis and reproductive glands. Correlations of other endocrine glands may correspond to a general physiological functional plan. The method of partial correlations is well adapted to the analysis of a series of characteristics and the determination of mutual relationships between pairs.

Visual fields, blind spots and the optic disc in endocrine diseases. Mayer, L. L. and H. R. Rony, Am. J. Ophth. **15**: 1024. 1932 Abst., J. Nerv. & Ment. Dis. **77**: 420.

The authors wished to study their patients with outstanding endocrine disease in order to determine if the optic discs, the peripheral fields for white objects and the blind spots showed any characteristic changes from the normal. The authors list 50 cases seen over a period of two years, including 6 cases of toxic goiter with basal metabolic rates from 35 to 55%, one case each of idiopathic pituitary tetany, congenital apituitarism, idiopathic tetany, myxedema, 12 cases of hypopituitarism, 11 cases of hypo-ovarism and 15 developmental anomalies. Of the entire series only one showed enlarged blind spots—a mental defective. Very marked contractions of the peripheral fields for white were demonstrated in five cases, all of which were proven hysteria. Four others showed a lagging of the image in the temporal fields and were considered as borderline visual fields. In no case of the entire series was a pathological disc found.

Abst., abbreviated.

Observations on hematopoietic hormone (addisin) in pernicious anemia. Morris, R. S., L. Schiff, J. H. Foulger, M. L. Rich and J. E. Sherman, Brit. M. J. **2**: 1050. 1932. Abst., J. A. M. A. **100**: 780.

The chief points to which Morris and his associates wish to draw attention in the treatment of pernicious anemia with liver and liver extracts are: (1) the small volume of material injected; (2) the prolonged and sustained reticulocytosis (duration thirty-four days); (3) the maturation of the red cells which eventually took place, and (4) the fact that a single injection produced such a sustained response. Technical difficulties are being encountered in the concentration of swine juice, but in time it is felt that these can be overcome so that material may be available for extensive clinical trial. Their results with human gastric juice have been confirmed by Conner and by Zerfas. The authors believe that the absence of addisin in the gastric juice in pernicious anemia is the cause for the reversion to a megaloblastic marrow in this disease. The lack of a satisfactory test for the presence of addisin in concentrated gastric juice, save its injection into a patient with pernicious anemia, is a handicap, as it has been in the case of liver extract and desiccated hog stomach. The authors are experi-

menting both biologically and chemically to try to overcome this difficulty. The observations they have made up to the present time indicate the probability that addisin is the physiologic hormone which maintains the normal state of the blood in health. They have under investigation the therapeutic effect of intramuscular injections of addisin in secondary anemias.

A clinical study of psychoses associated with various types of endocrinopathy. Notkin, J., Am. J. Psychiat. **12**: 331. 1932. Abst., J. Nerv. & Ment. Dis. **77**: 435.

The author feels that the occurrence of major types of psychoses in individuals with pronounced endocrinopathy is not as frequent as they are thought to be. The author found only eight cases in a state hospital population of 6,000 patients. Among them were 3 schizophrenics, 1 case of manic depressive psychosis, 1 case of epileptic psychosis and 3 hypophrenics. The author did not feel it advisable to include in his study cases with vague endocrine signs (reversed secondary hair distribution, diminished size and consistency of gonads) as in his opinion the relationship between the endocrine disorders and the mental manifestations in these cases is rather vague and the etiologic guesses offered by other workers are impressionistic. His study consists of a detailed biochemical and psychiatric investigation. The deviations in calcium, cholesterol and lecithin metabolism were minimal. The psychiatric study revealed a number of dynamic factors. The author feels, however, that although a psychologic dynamic interpretation of the mental reactions is desirable, it does not solve entirely the real problem of dementia praecox with or without endocrine disturbances.

Seasonal, endocrine and temperature factors which determine percentage metabolism per degree of temperature change. Riddle, O., G. C. Smith and F. G. Benedict, Am. J. Physiol. **101**: 88. 1932.

It is shown that the basal metabolism of various species and races of doves and pigeons markedly and similarly fluctuates with the seasons. The studies are based upon animals subjected to outdoor temperatures from April to November. They are given considerable protection from cold during the winter, and are subjected to air of greatest cooling power during autumn. Other earlier studies by Riddle have shown that the thyroids of these birds are larger and apparently more active in autumn and winter, and are smallest in summer; the gonads have the reverse relation to season. Nearly 350 metabolism measurements made on a single race of common pigeons at 15°, 20° and 30° C. during the four seasons show that the state of the animal—attained in connection with season—markedly influences the value of the metabolism at whatever environmental temperature this metabolism is measured. Further, at the various seasons the metabolism is quite unequally affected by measurement at environmental temperature either higher or lower than 20° C.; the metabolism of birds in summer being practically the same (change of 0.4% per degree) when measured at 20° or 30°, but the metabolism of summer birds measured at 15° shows an increase of nearly 2.5% for each degree of temperature change below 20°. Measurements made in autumn at the different temperatures give dissimilar relative changes; between 20°-30° the decline of the metabolism is 0.8% per degree, while from 20°-15° the change is 1.5% per degree. Though the point has not been tested it would logically follow that the so-called "critical" temperature will vary with the seasonal (and endocrine) state of the animal.

—Authors' Abst.

Relationship between internal secretions and sodium chloride content of bile (Einige Untersuchungen über die Beziehungen zwischen dem Chlor-spiegel in der Galle under der inneren Sekretion). Sasaki, K. J., Chosen M. A. **21**: 41. 1931. Abst., Chem. Absts. **26**: 5330.

Continuous feeding of thyroid increases the NaCl content of the fistula bile in a rabbit by stimulation of NaCl excretion and decrease in salt storage in the tissues. Intravenous injection of thyroxine produces a less pronounced change. When adrenaline is given, biliary NaCl is decreased, while the suppression of suprarenal activity by removal of the gland causes an increase due to the stimulation of hepatic excretion. Insulin also increases NaCl excretion by stimulation of bile flow and not by increased concentration of NaCl in bile. When NaCl is injected into the portal vein of an animal treated with insulin, NaCl concentration of the bile increases, showing that in the presence of excess

NaCl, insulin has a stimulating effect on salt excretion. Salt injection in the portal vein of a normal rabbit has no effect on blood NaCl, and produces a temporary slight increase in the biliary NaCl.

Normal organ weights (Zur Kenntnis des Normalen). Sitsen, A. E., Ztschr. f. Konstitutionslehre, **16**: 308. 1931.

The weights of the principal organs, including three of the ductless glands, of several hundred carefully selected normal adult cases from Java were compiled and correlated with each other and with the body as a whole. Three endocrine organs were included. The two suprarenals together weighed from 7 to 24 gm., averaging 14.5 gm.; the weight increased with stature, but showed no change with age. The two testicles together varied from 31 to 70 gm., averaging 49 gm.; the weight increased with stature and probably decreased after 35 years. A dozen normal thyroids varied from 16 to 49 gm., averaging 24 gm., which the author thinks is probably too low.—A. T. R.

On the effect of insulin, epinephrine and phlorihizin on the lactic acid content and the distribution of phosphates in the blood of rabbits. Yamada, S., J. Biochem. **17**: 61. 1933.

A study was made of the effect of insulin, epinephrine and phlorhizin on lactic acid and phosphate metabolism. Rabbits fasted for about 20 hours were used in the experiment. Ten to 50 units of insulin, 1 to 2 cc. of 1:1000 epinephrine, and 1 to 2 gm. phlorhizin were used in the various tests. Insulin was found to promote the synthesis of the hexose monophosphate at the expense of sugar, inorganic phosphorus and pyrophosphate. The resulting hypoglycemia caused decrease in the lactic acid content of the blood. Aside from causing slightly lowered inorganic phosphorus, epinephrine resulted in reverse reactions from insulin, as the pyrophosphate increased and the hexose monophosphate decreased. The hyperglycemia resulted in the splitting of glucose to lactic acid, thus causing a marked rise. Hyperglycemia from administration of glucose before insulin injection also caused increased lactic acid and pyrophosphate, but the hexose monophosphate showed slight increase. Phlorhizin produced no noticeable change in phosphate metabolism, though soon after its administration a slight rise occurred in inorganic phosphorus, followed by a decrease with time. Total phosphorus decreased markedly with epinephrine, phlorhizin and glucose administration.—Hazel M. Childs.

Placental enzymes in various stages of pregnancy. Abe, M. Jap. J. Obst. & Gynec. **15**: 44. 1932. Abst., Chem. Absts. **26**: 6002.

Glycerol or physiologic salt solution extracts of human placenta were used. Pepsin was present in human placenta in small amounts in every stage of pregnancy and the rise and fall during the pregnant periods was not marked. The enzyme decomposing glycine could not be proved to exist in the placentas at any gravid stage. Asparaginase was present in small amounts in the placentas of every stage of pregnancy.

Hormone control of changes in the endometrium during the menstrual cycle. Allen, E., Proc. Missouri State Medical Association. Abst., J. A. M. A. **99**: 334.

The changes that occur in the primate endometrium during the menstrual cycle have now been duplicated experimentally in ovariectomized monkeys by injections of ovarian hormones. It is possible, therefore, to revise the old classification of these changes, which was based entirely on histologic studies before the hormone control had been demonstrated. There are at least two hormones concerned: theelin, which reaches its highest concentration in the follicles but which is also found in the human corpus luteum, and progestin (Corner) or corporin (Hisaw) from the corpus luteum. Action of theelin is essential, for the corpus luteum hormone is ineffective when used alone. Therefore, the action of progestin or corporin is distinctly supplementary to that of theelin. Experiments with ovarian follicular hormone (theelin, estrin, folliculin, progynon) in laboratory rodents and monkeys have demonstrated that its principal action is to induce growth (hyperplasia) in the tissues of the genital tract, which is followed by the beginning of secretion of the glandular tissues. Theelin also influences the rate and amplitude of contraction of uterine

and tubal musculature. The follicular hormone, therefore, is responsible for the wave of growth which periodically runs through the whole genital tract and the mammay glands. But theelin alone fails to give a complete reaction in the endometrium. Progestin or corporin from the corpus luteum continues the endocrine action and produces the tortuous and twisted endocrine glands, the swollen cells and edematous stroma of the typical premenstrual endometrium. Paralleling this transformation, additional hypertrophy of the mammay glands occurs. These reactions, therefore, depend on one-two reactions of the theelin and progestin or corporin. Whether or not ovulation occurs, menstruation may appear at the expected time. Typical menstrual periods follow (1) removal of the ovaries, (2) injury of large follicles and (3) removal of corpora lutea. Similarly, experimental menstruation periods have followed several days after the cessation of long series of injections of follicular hormone. Menstrual bleeding usually does not occur during injections but begins (after a latent period of a few days) when they are stopped. From these experiments, menstruation is clearly degenerative in significance and follows a growth period resulting from the action of theelin. Although the corpus luteum hormones are necessary for the premenstrual transformation of the endometrium, they are not necessary for the process of menstruation itself. On the basis of its hormone control, the endometrial cycle may be divided into three periods: (1) postmenstrual, under the influence of theelin; (2) premenstrual, due to action of theelin and progestin or corporin together, and (3) menstrual, due primarily to decreased amounts of theelin.

Friedman's reaction for the diagnosis of pregnancy (La réaction de Friedman pour le diagnostic de la grossesse). Borras, P. E., Compt. rend. Soc. de biol. **111:** 819. 1932.

In 118 cases the pregnancy test with virgin rabbits was used. It was positive in all cases of pregnancy and negative under most other conditions. The exceptions were immediately after delivery, two cases of hydatiform mole, a case of chorioepithelioma, and two cases of cancer of the uterus.—J. C. D.

Sex physiology. VI. Ovulation induced by the luteinizing hormone, prolan B (Geschlechtsphysiologische Studien. VI. Ovulation ausgelöst durch das Luteinisierungshormon Prolan B). Borst, M., A. Döderlein and D. Gostimirovíc, München. med. Wchnschr. **78:** 1350. 1931. Abst., Chem. Absts. **26:** 3558.

Immature mice injected with an extract of the urine from a patient with carcinoma of the cervix uteri showed histological changes in the ovary indicating ovulation. The absence of large ripe follicles and the presence of luteinization indicated that the extract contained only prolan B. Prolan B is therefore capable of inducing ovulation in the absence of prolan A.

Effect of fuel oil on the secondary sex characters (Action du mazout sur les caractères sexuels secondaires). Buchheim, W., Compt. rend. Soc. de biol. **108:** 1210. 1931.

Young adult rats and guinea pigs received doses of oil either with their food or as subcutaneous injections. These animals showed, when autopsied after periods of three weeks or more, a marked shrinkage in the seminal vesicles. This is in agreement with the clinical experience that libido is reduced in men exposed to oil fumes.—J. C. D.

Further consideration of the properties of the gonad-stimulating principle of mare serum. Cole, H. H., H. R. Guilbert and H. Goss, Am. J. Physiol. **102:** 227. 1932.

Data are presented regarding the effect of the gonad-stimulating hormone upon male and female rats. Data are also given on the stability of the hormone. Series of 300 to 400 rats were used. The effects upon the male reproductive organs were very similar in general to those produced by prolan or by anterior pituitary implants. Impotency was temporarily cured in male rats which were on a low protein diet. The hypophyses of the impotent rats were smaller and contained a smaller amount of gonad-stimulating hormone than did the hypophyses of litter-mate controls on a normal diet. A given amount of hormone had as pronounced an effect upon the ovaries of immature female rats when given as a single dose as when given in several doses. A method of assay

of the hormone using immature rats is given. The hormone will produce ovulation in the immature rat when small doses are given. It was found that the hormone as it occurs in serum is relatively stable in acid and alkali (pH2 to pH 10) and is not easily destroyed by oxidation or by pepsin.—Authors' Abst.

Artificial induction of ovulation and oestrum in the ewe during anoestrum. Cole, H. H. and R. F. Miller, Am. J. Physiol. **104**: 165. 1933.

Sixty-one ewes were injected with the gonad-stimulating hormone of mare serum in an attempt to induce ovulation and oestrum during anoestrum. Ovulation was produced by a single injection of 50 R.U. or more of gonad-stimulating hormone. However, using this procedure, the ewes did not come into oestrum. Further, when injections were made on several consecutive days the ewes did not exhibit oestrum, but when a second injection followed the first after an interval of 16 days (the oestrous cycle in sheep is about 17 days long) both ovulation and oestrum were produced. A high percentage of fertile matings resulted. In another group in which the second injection was made 14 instead of 16 days after the first, only 2 of 15 ewes came into oestrum. A third injection 16 days after the second resulted in 8 of 13 ewes coming into oestrum on the second day following injection. The evidence leads to the conclusion that the cyclic phenomena associated with the oestrous cycle are activated by a single injection of gonad-stimulating hormone, but that a second stimulus (injection) must be applied after a specific time interval in order that all the events associated with oestrum may be manifested. Therefore, the results show that the administration of sufficient amounts of the gonad-stimulating hormone at proper time intervals will result in oestrum, ovulation, and impregnation following breeding during the anoestrous period.—Authors' Abst.

The effect of castration at various ages upon the adult weight of male albino rats. Commins, W. D., J. Exper. Zoöl. **63**: 573. 1932.

Castration of male albino rats at the ages of 20, 50, 90, 130, and 170 days had an inhibiting effect upon their rate of growth as measured by body weight at 165 and 256 days of age, respectively. All castrate groups were lighter in weight than the non-castrate groups. The earlier the age at which castration took place, the greater was the inferiority in weight when comparison was made with non-castrate animals. There is no indication from the present data that there is anything like a critical stage in the physiological development of albino rats, beyond which castration is wholly without effect upon weight.
—Author's Abst.

Delayed pregnancy in mice. Enzmann, E. V., N. R. Saphir and G. Pincus, Anat. Rec. **54**: 325. 1932.

Each young suckling mouse prolongs the gestation of its pregnant mother by 21 hours on the average. The available data on pregnant lactating rats indicate that a similar prolongation occurs in this species. Delayed pregnancy is due to the failure of the blastodermic vesicles to become implanted at the normal time. Late implantation may occur from the end of the seventh to the sixteenth day after mating. The greater the number of suckling young the later the implantation. Blastocysts, the implantation of which is delayed, remain in the uterus in a relatively quiescent state. They enter the uterus at the normal time and develop at the same rate as undelayed blastocysts until the end of the sixth day after mating. Lactating females which have copulated at parturition may fail to produce any embryos. This may be due to failure of ovulation, or, in some cases, to failure of implantation. The sojourn in the uterus of free blastocysts beyond a certain period may lead to their degeneration. A brief description is given of the uterine events occurring before and at implantation. The actual implantation process in delayed implants is essentially like that of undelayed blastocysts.—Authors' Abst.

A study of the estrus-producing hormone in the circulating blood of normal women. Ford, F. A. and S. C. Mueller, Am. J. Obst. & Gynec. **24**: 329. 1932.

Cyclic variation of estrus-producing hormone in the circulating blood was investigated by injecting oöphorectomized white mice with a hormone-containing extract (method of Frank) prepared from blood taken semi-weekly (over one to three months) from five regularly menstruating women. In 71 tests

(not performed in duplicate) five mice died during administration of the extract, spontaneous oestrual cycles occurred in three instances and results in the remainder indicated that positive reactions may occur at any time in the cycle, with the increase in hormone concentration of short duration (no consecutive positives during premenstrual periods), while negative results are frequent during the premenstrual period. The authors conclude that a positive reaction is of value in determining functional activity of the ovaries, but a negative reaction is of little diagnostic or prognostic significance.—Minna Emch.

The production of functional corpora lutea unilaterally by the direct intrafollicular injection of extracts of urine of pregnancy. Friedman, M. H., Am. J. Physiol. **101**: 34. 1932.

In earlier experiments it was found that follicles injected with small amounts of extracts of urine of pregnancy developed into corpora lutea in the absence of any general humoral change of sufficient magnitude to produce any discernible change in the ripe follicles in the contralateral, untreated ovary. All attempts to demonstrate some functional activity on the part of these unilateral corpora lutea, however, proved futile. The present experiments were designed to discover the reasons for the lack of functional manifestation on the part of these unilateral lutein bodies. Briefly, the results of the present experiments may be summarized as follows: (1) In about one-third of the animals in which the contralateral (untreated) ovary was removed 24 hours after the intrafollicular injection, the unilateral corpora lutea so produced proved to be functional (decidual reaction). The incidence of functional corpora lutea was equally as great, however, in a series of animals in which the untreated ovary was left in situ. It is evident, therefore, that the presence or absence of the untreated ovary is not of great significance in this regard. Moreover, if there exists a physiological antagonism between the secretion of ripe follicles and the secretions of corpora lutea, such antagonism was not evident under the conditions of these experiments. From a series of control experiments it is apparent that the failure to secure a greater percentage of functional corpora lutea is to be attributed to the operative procedures. Hence, it is probable that the better results obtained in these experiments as compared with those of last year are to be credited to an improvement in technique which the operator himself did not appreciate.—Author's Abst.

The male hormone; the effect of the male hormone and the anterior pituitary. Funk, C. and B. Harrow, Am. J. Physiol. **101**: 218. 1932.

Rats around a month old were divided into four groups: (1) controls; (2) injected with the male hormone; (3) injected with the anterior pituitary; (4) injected both with the male hormone and the anterior pituitary. The animals were killed at the end of four days. During the experimental period the animals received daily injections of 0.5 cc. of an extract of male hormone (equivalent to about 600 cc. male urine) and a twice daily injection of 0.3 cc. of the urine of pregnant women. The controls showed not only small seminal vesicles (s.v.) but there was very little glandular development and hardly any secretion. The s.v. of the animals injected with the male hormone were somewhat larger and they contained more secretion. Somewhat larger were the s.v. of the animals injected with the urine of pregnant women, and they showed a little more secretion. Instances in which the rats received both the male hormone and the urine of pregnant women, the pictures of the s.v. were outstanding; the organs were large, there were many ramifications of the glandular structure, and there was much secretion. In comparison with the striking picture exhibited by the s.v. the other organs did not show much. There was no spermatogenesis in any of the animals. The ductus deferens did not show a characteristic reaction. The number of mitotic figures in the spermatogenes increased with the increase in size of the s.v.—B. Harrow.

Organotherapy of mastodynia. Gabrielianz, A. G., Am. J. Obst. & Gynec. **25**: 499. 1933.

Eight cases are reported in support of the thesis that the cause of mastodynia lies probably in overactivity of the corpus luteum due to hyperfunction of the anterior pituitary. Five of the patients were cured by administration of ovarian residue and two by the use of "female sex hormone" by mouth and subcutaneously. In one patient the pain in the breasts was not relieved.—R. G. H.

The presence of the female sex hormone in urine (Über das Vorkommen von weiblichem Sexual hormon im Harn). Glimm, E. and F. Wadehan, Biochem. Ztschr. **243**: 97. 1931. Abst., Chem. Absts **26**: 1967.

The authors reported finding 500 mouse units of the sex hormone in male urines and up to 1000 units in the daily urines from non-pregnant females. Inasmuch as these results are considerably higher than those reported by other observers, they point out certain steps in their technic which have been instrumental in preventing hormone loss. The urines were dialyzed for 24 hours in filter thimble, then concentrated to about one-third to one-fourth of the original volume and injected in this condition. The dialysis removes the toxic substances from urine without losing much of the hormone.

The relation of pregnancy cells in the pituitary of the rat to the reproductive cycle. Haterius, H. O., Anat. Rec. **54**: 343. 1932.

Pregnancy cell types appear in the anterior lobe on the third and fourth day following fertile or infertile copulation. These cell types increase in number and in size until the twelfth day, and, in the event of pregnancy, persist throughout the time of gestation. In all instances they disappear upon resumption of the oestrous cycle. The pituitary of the pseudopregnant animal is identical in its changes with that of pregnancy. The pregnancy cell type in this circumstance persists until the twelfth day—the length of the pseudopregnant period—disappearing upon the return of estrus. Pregnancy cell types occur coincidental with a dominant luteal ovarian phase and, it is believed, on the basis of this and from previous experimental evidence, that the luteal factor is responsible for their genesis. Their significance, however, remains obscure.
—Author's Abst.

Simple test for pregnancy using immature female albino rats; premature establishment of vaginal orifice by intraperitoneal injections of urine of pregnant women. Kelly, G. L., J. A. M. A. **100**: 1010. 1933. Abst., A. M. A.

The author points out that intraperitoneal injections of from 5 to 15 cc. of urine from pregnant women will cause premature establishment of the vaginal orifice in the albino rat weighing from 30 to 40 gm., usually within from 72 to 84 hours. Intraperitoneal injections of the same amount of urine from non-pregnant women will not cause such premature opening of the vagina. Two animals should be used and the opening of the vaginas of both is read as positive; of one, as doubtful (the test should be repeated); of neither within 96 hours, as negative. If the vagina is open and the orifice obscure, one may see it by holding the animal by the neck and shoulder region and pulling strongly on the base of the tail. In this maneuver the abdomen should not be compressed. The main advantages are the simplicity of the test and the ease of reading the result.

Oestrous rhythm of vegetarian and omnivorous rats. Lin, K. H., C. Tsai and S. Wan, Chinese J. Physiol. **6**: 23. 1932. Abst., Chem. Absts. **26**: 5994.

The oestrus cycle is not affected by the mild nutritional deficiency of a good vegetarian diet but is lengthened with a poor vegetarian diet. The dioestrus intervals are prolonged. The cornified-cell stage is not affected.

Pigmentation of the mammary region of the hyperfeminized male guinea-pig (A propos de la pigmentation de la région mammaire chez le Cobaye mâle hyperféminisé). Lipschütz, A., Compt. rend. Soc. de biol. **108**: 848. 1931.

A considerable black pigmentation in the mammary region around the nipple takes place in the male guinea-pig after hyperfeminization by ovarian transplantation. Pigmentation occurs only in these cases in which the field around the nipple is surrounded by yellow, red or black hair, and is absent in albinotic guinea-pigs, or in a field surrounded by albinotic hair in colored guinea-pigs. Only if the nipple is pigmented from the beginning there can be in the hyperfeminized animal a highly pigmented field surrounded by albinotic hair. All these statements are in full accord with the experiments of Bloch; pigmentation takes place only in a territory predisposed.—Author's Abst.

Diagnosis of hypogonadism in the male. McCullagh, E. P., Proc. Central Society for Clinical Research, Abstract J. A. M. A. **100**: 70. 1933.

A method for the assay of blood and urine for testicular hormone has been described, and has been used as a laboratory test for hypogonadism. The clinical signs and symptoms of testicular insufficiency are rather indefinite. Approximately 50% of the patients diagnosed clinically as having hypogonadism have been found to have a normal quantity of the hormone in their urine. The symptoms of patients who are excreting a normal amount of hormone are not relieved by the injection of additional amounts of hormone. The urine of women also contains a very definite amount of a substance which will promote the growth of the comb of a capon. Several oöphorectomized women have been found to excrete this substance. Eunuchs do not excrete male sex hormone. There is evidence to indicate that women suffering from hypertrichosis excrete large quantities of comb-growth-promoting substance.

Studies on the physiology of lactation; lactation in the male guinea pig and its bearing on the corpus luteum problem. Nelson, W. O. and G. K. Smelser, Am. J. Physiol. **103**: 374. 1933.

Three castrate and 5 experimental cryptorchid male guinea pigs which had carried functional ovarian grafts for periods of time ranging from three to ten months were induced by the administration of an extract of the anterior hypophysis. This reaction was induced with equal facility in 5 other cases when the graft was removed prior to the initiation of treatment. Other experimental cryptorchid animals were injected with pyramided amounts of oestrin for eleven weeks. When this treatment was followed by pituitary administration, lactation resulted. It is concluded that, in the male guinea pig, lactation may be induced in the absence of any luteal influence operating on the mammary glands. The idea is advanced that normal lactation and some cases of experimental lactation may be explained on the basis of a release of the lactation-inducing factor by the removal of the ovarian influence on the anterior hypophysis.—R. G. H.

Male hormone. I. The hormone in the urine of males. Ogata, A. and Y. Ito, J. Pharm. Soc. Japan. **52**: 674. 1932. Abst., Chem. Absts. **26**: 5638.

A modified continuous extraction apparatus was used. The amount of the male hormone in the urine varies with the season, and it is possible to extract the hormone of the urine with chloroform after a very small amount of sulfuric acid has been added. Better results are obtained by heating the urine before extraction.

The action of corpus luteum extracts containing progestin on uterine motility in the unanesthetized rabbit. Reynolds, S. R. M. and W. M. Allen, Am. J. Physiol. **101**: 87. 1932.

After the first few days of pseudopregnancy in the rabbit, the uterus is both quiescent and refractory to the normal stimulating action of oestrin (theelin). Removal of the ovaries at this time renders the uterus readily susceptible to small amounts of theelin. In the present experiments it has been found that progestin, an active extract of the corpus luteum which induces endometrial proliferation is capable of inhibiting the stimulating action of theelin (up to 1000 rat units per kilogram of body weight), provided a sufficient amount of progestin is employed (4.8-5.0 rabbit units). By the use of smaller amounts of progestin (1.6 rabbit units) the response to 100 rat units of theelin is inhibited, but by giving 500 rat units of theelin the normal theelin response may be obtained. It has also been found that progestin can overcome the spontaneous motility of the oestral (post partum) rabbit. These data in vivo in the unanesthetized rabbit provide adequate replacement-therapy evidence that the action of the corpus luteum is inhibitory to uterine motility, and that it is antagonistic in this respect to the action of oestrin (theelin).—Authors' Abst.

Influence of the gonads on protein metabolism; urinary creatinine after castration. Schrive, I. and H. Zwarenstein, Biochem. J. **26**: 118. 1932. Abst., Chem. Absts. **26**: 3828.

Castration of adult male rabbits causes an increase (25-50%) in the urinary creatinine. The creatinine output falls to the normal pre-castration level when testes are grafted into castrated rabbits. Subsequent removal of the graft again leads to an increased creatinine output.

Changes in the composition of the blood and in the tone of the vegetative nervous system in cows during pregnancy and parturition (Die Änderungen in der Blutzusammensetzung und im Tonus des vegetativen Nervensystems während der Gravidität und in der Geburtsperiode des Rindes). Seekles, L., B. Sjollema and F. C. Van der Kaay, Biochem. Ztschr. **249**: 424. 1932. Abst., Chem. Absts **26**: 5138.

In pregnant cows until about four days before parturition there are no noteworthy alterations in the mineral composition of the serum. About this time, however, the calcium and the inorganic phosphorus of the serum begin to diminish, and during parturition and shortly afterwards their level may rise or fall, indicating a liability of the mechanism for mineral regulation. The lowest calcium and phosphorus values are obtained either just before or just after parturition, while the magnesium is increased at the same time. The serum potassium diminishes and reaches the lowest value a few days after parturition. The blood sugar increases during the parturition. The acetone bodies also increase a few days before and after parturition, but during the latter it varies greatly. Generally, a high content of acetone bodies coincides with a low sugar level and vice versa. There are no changes in the non-protein nitrogen of the blood. A case of atypical parturition paresis has been observed where the symptoms did not develop at the time the serum calcium level fell lowest but when this had already increased considerably. The paresis could be overcome within 90 minutes by an intravenous injection of parathyroid extract, and although the total calcium level had actually diminished somewhat the ionizable calcium fraction increased two-fold, and the disappearance of the muscle atony is attributed to the tonic effect of calcium ions in the muscles. It is not certain, though, whether this effect of the calcium ions is direct or indirect. There seems to develop with the progress of gravity a relative increase in vagus tonicity of the heart which disappears again after birth, but only in one instance was it possible to show that this is accompanied by a rise in the K/Ca ratio, so that the hypervagotonia is the result of other factors as well.

Lutein tissue and male sex characters (Luteingewebe und männliche Geschlechtscharaktere). E. Steinach and H. Kun, Pflüger's Arch. f. d. ges. Physiol. **227**: 266. 1931.

It has been shown previously by Lipschütz in the guinea-pig and by Sand in the rat that the clitoris of the female can be transformed by testicular transplantation into a penis-like organ. The authors show that the same can be obtained by exposing the ovary of the guinea-pig to x-rays or by treating guinea-pigs with hypophyseal hormones or luteal extracts. It is concluded that this particular action of the x-rays or of the hypophyseal hormones is due to extensive luteinization of the ovary—A. Lipschütz.

Experimental investigations on the transplantation of ovaries which have been kept at low temperatures (Experimentelle Untersuchungen über die Transplantation von Eierstöcken, die bei niedrigen Temperaturen konserviert wurden). Üprus, V. With an introductory note by A. Lipschütz. Folia neuropath. estoniana, **12**: 15. 1932.

Ovaries which had been kept for one or more days at temperatures lower than zero were engrafted into 33 castrated male and female guinea-pigs. There was never an endocrine effect on the nipples or the vagina. On the contrary, when using fresh ovary with the same intrarenal technic "takes" were secured in 11 of 13 experiments. Similarly, ovaries which were kept at temperatures of 0° to 10° C. for one to three days, were engrafted into 26 castrated male guinea-pigs; there were 13 "takes" with evidence of endocrine activity. It appeared that when an ovary has been kept outside the body and afterwards engrafted the percentage of "takes" is diminished and the latent period between grafting and beginning of endocrine activity is lengthened.—A. Lipschütz.

Influence of the follicular hormone on the plumage of the pigeon and of Vanellus chilensis (Influence de la folliculin sur le plumage du pigeon et du Vanellus chilensis). Vinâls, E., Compt. rend. Soc. de biol. **109**: 1332. 1932.

The experiments of Lipschütz have been repeated with the difference that the follicular hormone has been injected daily with the purpose of maintaining as far as possible a constant level of the follicular hormone in the blood. Four animals received each during 10 days 7500 R.U. of follicular hormone from the urine of pregnant women. The feathers newly grown after plucking revealed a quite normal appearance. Similar experiments were performed on Vanellus chilensis, popularly called "queltehue." This Chilean species shows a great variety of colors; there is, like in the pigeon, no sexual dimorphism. The adult animal weighed 350 gm. Two daily injections of the folliculine were made during 25 days, the animal receiving a total quantity of 15,000 R.U. The feathers newly grown after plucking were normal. These experiments are in favor of the thesis of Lipschütz that in certain species without sexual dimorphism the feather is not subject to the influence of the follicular hormone.—A. Lipschütz.

Hysterectomy and the structure of the ovary (Les répercussions de l'hystérectomie sur l'histophysiologie ovarienne). Watrin, M. and H. Brabant, Arch. de biol., Paris, **43**: 153. 1932. Abst. Physiol. Absts. **17**: 530.

The authors maintain that the sexual motor is not the anterior pituitary, but the ovarian follicle, both ovum and follicular epithelium. Experimental removal of the uterus involves interstitial involution of the ovaries and the suppression of sexual behavior. In immature and mature rabbit's removal of the uterus is followed by transformation of the ovary into a large mass of interstitial epithelioid cells charged with lipin. In the mature rabbit after removal of the uterus no true functional corpus luteum remains. Clinically it is suggested that removal of the uterus produces a slow equivalent to the more dramatic results of castration.

The effect of theelin injections on the castrated woman. Werner, A. A. and W. D. Collier, J. A. M. A. **100**: 633. 1933.

Studies are reported on five women 22 to 40 years of age, from whom the ovaries had been removed. Theelin was given in increasing doses from 200 to 800 rat units daily. It restored the breasts and genital tract of the women to apparently the normal sexual state from the previous castration atrophy. The changes in the atrophied endometrium approximated or equalled the interval changes found in the normal women at the time of ovulation. It did not produce the pregravid changes in the endometrium. The bleeding from the uterus of castrated women induced by theelin occurred from an endometrium approximating or equalling in development the interval changes found in the uteri of normal women. The bleeding was qualitatively indistinguishable from menstruation in normal women. It was accompanied by the subjective symptomatology usually experienced by normal women during menstruation. The theelin relieved the subjective symptoms that occurred following castration. Four women stated that "libido was markedly increased."—R. G. H.

Thyreotropic hormone of anterior pituitary. Anderson, E. M. and J. B. Collip, Proc. Soc. Exper. Biol. & Med. **30**: 680. 1933.

The authors have prepared highly purified extracts of the anterior pituitary containing the thyreotropic hormone. Administered to hypophysectomized rats it prevented the thyroid atrophy which occurs in such animals untreated. The extract causes an increase in the basal metabolic rate in rats and guinea pigs and marked hyperplasia of the thyroid glands.—M. O. L.

Influence of anterior lobe of hypophysis on blood sugar content (Über den Einfluss des Vorderlappenhormon auf den Blutzuckerspiegel). Böhm, F., Ztschr. f. d. ges. exper. Med. **84**: 689. 1932. Abst., J. A. M. A. **100**: 231.

Tests on rabbits convinced Böhm that the intravenous injection of 100 units of prolan produces a hyperglycemia. The intramuscular injection is less effective, and the subcutaneous administration of the same quantity has no effect whatever. The hyperglycemia produced by prolan reaches its maximum from 20 to 50 minutes after the injection and is still present after ninety minutes,

but it can be suppressed by ergotamine. The injection of prolan also reduces the hypoglycemia produced by insulin. Glycosuria follows the administration of prolan only if the blood sugar content increases 300 mg. per hundred cubic centimeters. Tests to determine the origin of the blood sugar following the injection of prolan is not followed by hyperglycemia if the liver is entirely free from glycogen. These observations indicate the possibility of an involvement of the anterior lobe of the hypophysis in metabolic regulation.

Nitrogen metabolism in the hypophysectomized dog. Braier, B., Anales farm. bioquím. **3**: 24. 1932. Abst., Chem. Absts. **26**: 5631.*

The urinary and fecal N elimination in fasting hypophysectomized dogs is about 30% below the normal. The creatinine elimination of non-fasting operated dogs is 9-18% and of fasting dogs 30-35% below normal. Other phases of the urinary N and creatinine metabolism in the hypophysectomized dog and the effect of the operation on the sugar metabolism were also studied.

Blood pressure in hypophysectomized dogs (La presión arterial de los perros hipofisoprivos). Braun, M. E., Rev. Soc. argent. de biol. **8**: 463. 1932.

Totally hypophysectomized dogs (16 animals) had a lower maximal pressure (average of numerous determinations 108 mm. Hg.) than normal controls (average 130 mm. Hg.). Extirpation of the posterior lobe (4 dogs, 29 determinations) did not reduce the blood pressure significantly (120 mm. Hg.), neither did cauterization of the tuber cinereum (average of 12 dogs: 124 mm. Hg.). It is supposed that the lack of a secretion from the anterior lobe influences the vasomotor reflex mechanism.—J. T. L.

Contribution to the quantitative study of the hormones from the anterior lobe pituitary by use of the adult rabbit; application of biologic measure to the gonadotropic hormone (Contribution a l'étude quantitative de l'action des hormones pré-hypophysaires chez la Lapine adulte; application au titrage biologique de l'hormone gonadotrope). Brindeau, A., H. Hinglais and M. Hinglais, Compt. rend. Soc. de biol. **111**: 582. 1932.

Rabbits respond to the gonadotropic hormone. The minimum dose sufficient to produce corpora hemorrhagica 48 hours after one intravenous injection in animals of about 2 kilo weight was called a rabbit unit. In 30 animals it varied from 10 to 20 mouse units and averaged 15.—J. C. D.

Estimation of the antidiuretic potency of pituitary (posterior lobe) extract. Burn, J. H., Quart. J. Pharm. & Pharmacol. **4**: 517. 1931. Abst., Physiol. Absts **17**: 443.

A method is described for estimating the antidiuretic potency of pituitary extracts by determining the delay which is produced in the excretion of water. Four groups of four male rats, which had been deprived of food overnight, were given by stomach tube warm water in a quantity of 5 cc. per 100 gm. body weight, and each rat immediately after receiving the water was injected subcutaneously with pituitary extract. Two of the groups were given the extract being tested, and the other two groups were given an extract of the international standard pituitary powder. The rats were placed in metabolism cages, four in each cage, and the output of urine was measured at intervals of 15 minutes after the first appearance of urine. For each group of four rats there was determined the time between the administration of the water and the point of maximum rate of excretion of this water. The experiment was repeated two or three days later, giving the test extract to the rats which had received the standard in the first experiment and vice versa. The average time between administration and point of maximum rate of excretion for both standard and test extracts has thus been determined in the 16 rats, and the antidiuretic potency of the test extract can be given in units of the international standard pituitary powder by reference to a characteristic curve. The dose of pituitary extract used for rats of 200 to 300 gm. was of the order of 0.006 units per 100 gm. body weight. Four commercial extracts examined by this method had antidiuretic potencies ranging from 9 to 20 units per cc. compared with oxytocic activities of 10 to 18.5 units per cc. The antidiuretic potency of each of these extracts did not vary from its oxytocic potency by more than the experimental error.

Follicular atresia in the ovaries of hypophysectomized salamanders in relation to yolk formation. Burns, R. K., Jr., J. Exper. Zool. **63**: 309. 1932.

The atresia which prevails in the ovaries of hypophysectomized salamanders affects only follicles which have attained a diameter of 400 mu. In animals hypophysectomized while immature, no follicles are able to exceed this size; in older animals all above this size degenerate. The critical size falls just before the beginning of yolk formation. Although atresia may occur in the ovaries of salamanders for various causes, it is here attributed to hypophysectomy for the following reasons: (1) Control specimens reared in the same aquarium under identical conditions did not show atresia. (2) Growth was not inhibited after hypophysectomy; instead the animals attained adult size but little later than controls. Evidently the effect is not due to a general inhibition of development. (3) The time at which atresia attacks the follicle coincides with the period when the ovaries of young salamanders become highly susceptible to stimulation by administration of extracts containing the gonad-stimulating substance of the hypophysis, and by implantations of the anterior lobe. For reasons discussed, the deficiency responsible for atresia is assumed to be the gonad-stimulating substance, rather than the growth-promoting substance. The process of atresia, with the accompanying pronounced eosinophilia, is described.
—Author's Abst.

Conservation of the oxytocic properties of powdered posterior lobe of the hypophysis (Conservation de l'activité ocytocique de la poudre de lobe postérieur d'hypophyse). Choay, A. and L. Wurmser, Compt. rend. Soc. de biol. **110**: 1188. 1932.

Beef gland was prepared by desiccation in vacuo over sulphuric acid in the cold. It was stored in colorless glass bottles in the light, but protected from moisture by stoppers containing quick lime. After two years it retained at least 85% of its original oxytocic powers when tested on guinea pig uterus.—J. C. D.

The effect of an acid extract of the anterior pituitary gland upon the iodine concentration of the blood and thyroid gland. Closs, K., L. Loeb and E. MacKay, J. Biol. Chem. **96**: 585. 1932.

The authors studied the effect of injections of acid extract of cattle anterior pituitary glands upon the total iodine content, and upon the organic and the inorganic fractions in the thyroid gland and in the blood of guinea pigs. The iodine determinations were made according to the method of v. Fellenberg as modified by Closs. They found that after 5 intraperitoneal injections of 1 cc. each day given over a period of six days the average weight of the thyroid glands of the injected animals was 94% greater than the average weight of the glands of normal guinea pigs. The average total blood iodine for 19 control bloods was 16 gamma per cent, and for 23 bloods from injected animals was 41 gamma per cent. The average of the alcohol insoluble or organic iodine fraction in the blood of the normal animals was 19, whereas the average in the injected guinea pigs was 41 gamma per cent. There was no significant change in the alcohol soluble or inorganic iodine fraction in the blood. The average total iodine content in the thyroid glands of the normal animals was 29 mg. per cent, whereas the total iodine content in the thyroids of the injected animals averaged 10 mg. per cent. The average of the organic iodine fraction in the thyroid gland for the control thyroids was 28.5 mg. per cent and in the thyroids of the injected animals was 7.2 mg. per cent. There was an increase in the alcohol soluble iodine content of the thyroid glands of the injected animals. The authors conclude that the injection of acid anterior pituitary extracts of cattle causes an increase in the organic iodine fraction in the blood at the expense of the organic iodine of the thyroid gland and that these changes in the iodine metabolism correspond to those noted in Graves' disease in man.—W. J. Siebert.

The inhibition of oestrus by extracts of the anterior lobe of the pituitary body. D'Amour, Marie C. and H. B. Van Dyke, J. Pharmacol. & Exper. Therap. **47**: 269. 1933.

Young mature female rats were used. The mean length of estrus in 674 cycles in 112 rats was 4.39± 1.40 days. The extracts were made by the authors' methods, previously described, from beef and sheep glands. Extracts from sheep were consistently more potent in ovary stimulation and oestrus inhibition. Extracts made from other tissues were inert.—C. I. R.

An examination of cerebrospinal fluid, by means of the uterine fistula, for the presence of the oxytocic factor of the posterior pituitary. Friedman, Gertrude Sanders and M. H. Friedman, Am. J. Physiol. **101:** 35. 1932.

The use of the uterine fistula technique for the detection of the oxytocic factor of the posterior pituitary removes the difficulties inherent in the isolated strip method. The fistula preparation will not respond to the intravenous injection of non-specific fluids or proteins, nor to the injection of calcium salts histamine (except possibly, in large amounts—40 mg. and 0.5 mg., respectively). The isolated strip, on the other hand, responds to minute quantities of any of these in a way indistinguishable from its response to pituitrin. The intravenous injection of cerebrospinal fluid obtained by cisternal puncture from normal dogs has never given the slightest response in the fistula. Yet, the sensitivity in each case was such that a definite response should have been obtained even if the cerebrospinal fluid contained only the lowest concentration given by Dixon for the oxytocic factor (0.02 International units per cc.). Experiments are now in progress with alcoholic extracts of human cerebrospinal fluid which are designed to indicate if there is in human cerebrospinal fluid any pituitary-like oxytocic material in the much smaller concentrations postulated by workers other than Dixon.—Authors' Abst.

The hormone of the anterior lobe of the hypophysis. Fukui, S. and M. Murata, Tr. Jap. Path. Soc. **21:** 152. 1931. Abst., Chem. Absts **26:** 6003.

Extracts of placenta and of the anterior lobe of the hypophysis have the same biologic reaction, causing the formation of corpus luteum in the ovary after their injection into young female animals. These two extracts differ in resistance to heating, alkali and acid. From this it is concluded that they differ in chemical structure.

Action of extract of posterior lobe of pituitary after intramuscular injection into cervix uteri. Heller, T., Polska gaz. lck. **11:** 124. 1932. Abst., J. A. M. A. **98:** 1520.

It is generally known that solution of pituitary, injected hypodermically or intramuscularly, begins to act after from five to ten minutes. Heller obtains contraction of the uterus in from five to ten seconds by injecting 1 cc. of the drug directly into the cervix uteri, as a routine in postpartum hemorrhage and also when there is bleeding after vaginal cesarotomy or after curettage. The results are reported satisfactory in about 2,000 cases that have been noted by the author during the last eight years.

Pituitary and thyroid. VIII. Anterior pituitary lobe extract on weight of thyroid (Hipófisis y tiroides. VIII. Acción del extracto de lóbulo anterior de hipófisis sobre el peso de la tiroides). Houssay, B. A., A. Biasotti and P. Mazzocco, Rev. Soc. argent. de biol. **8:** 122. 1932.

Evans and Simpson's (1931) alkaline anterior pituitary extract was injected into the peritoneal cavity of dogs in daily doses of 10 cc. (=3.4 gm. fresh gland). The activity of the extract was controlled by determining its power to increase the weight of adult rats whose weight had remained constant prior to the treatment. Twelve dogs treated for short periods (1 to 6 days) had definitely heavier thyroids than the normal average. In 7 dogs the right thyroid was removed and 7 to 20 days later the left thyroid was taken out; in 5 cases the second thyroid was from 8 to 32% heavier than the first. The same procedure was followed in 13 dogs which received during the interval between the two thyroidectomies a daily intraperitoneal injection of anterior pituitary extract. The difference in weight between the thyroids was considerably more marked; the left weighed from 23 to 212% more than the right. The greatest effect was observed in those animals treated for longer periods (11 to 24 days). Puppies also showed a greater increase in thyroid weight under similar conditions (2 experiments). Three hypophysectomized dogs had the right thyroid removed and were treated with anterior pituitary extract for 6 days; the left thyroid was then removed and increases in weight of 10.5 and 48% were observed.—J. T. L.

Hypophysis and thyroid. XII. Effect of anterior lobe extract, on blood iodine (Hipófisis y Tiroides. Acción del extracto anterio-hipofisario sobre la iodemia). Houssay, B. A., P. Mazzocco and A. Biasotti, Rev. Soc. argent. de biol. **8**: 321. 1932.

Evans and Simpson's growth-promoting factor was injected into dogs over a period of 1 to 29 days. A considerable increase in blood iodine was observed. —J. T. L.

Hypophysis and thyroids. XIII. Thyroid of rats in parabiosis and injected with anterior pituitary extract (Hipófisis y tiroides. XIII. Reacción de la tiroides de la rata en parabiosis o inyectada con extracto anterohipofisario). Houssay, B. A., Rev. Soc. argent. de biol. **8**: 411. 1932.

Injections of anterior pituitary lobe extract produced no histological signs of hyperactivity nor increase in weight of the thyroid. The thyroids of normal rats united in parabiosis with a thyroidectomized rat showed no change. The rat is not a convenient species for the study of the action of the anterior pituitary hormone on the thyroid.—J. T. L.

Pituitary and metabolism (Hypophyse et metabolism). Houssay, B. A., Rev. franç. d'endocrinol. **9**: 423. 1931.

Based largely on the examination of literature the author concludes that the hypophysis plays an important rôle in metabolism, the "hypo" condition resulting in lower basal metabolism and its "hyper" condition increasing basal metabolism. The effects are variable in different species. The hypophysis stimulates the consumption of endogenous proteins and their transformation into sugar.—B. C.

Rôle of the hypophysis in adrenaline and morphin hyperglycemia (Papel de la hipófisis en las hiperglucemias adrenalínica y morfínica del sapo). Houssay, B. A. and E. Di Benedetto, Rev. Soc. argent. de biol. **8**: 448. 1932.

In toads (Bufo arenarum) the fasting blood sugar was slightly lowered by extirpation of the anterior pituitary lobe and hyperglycemia produced by adrenaline and morphia was considerably less marked. Implantation of the anterior pituitary lobe into normal animals increased the hyperglycemia produced by these drugs; implantation into operated animals made them react as normals. The posterior lobe (intermediate and neural substances) proved less active than the anterior lobe.—J. T. L.

Amount of so-called hypophysis hormone in the blood and urine in pregnancy. Iimuro, S. and M. Murata, Tr. Jap. Path. Soc. **21**: 156. 1931. Abst., Chem. Absts. **26**: 6003.

The increase of so-called hypophysis hormone in blood and urine in pregnancy is proportionate to the growth of placental trophoblasts; i.e., it is most abundant at the third month of human pregnancy. Hence the origin of so-called anterior-lobe hormone in blood and urine during pregnancy may be the trophoblasts of the placenta.

Action of the posterior lobe of the hypophysis in headache. Letter, J. A. M. A. **100**: 753. 1933.

Carnot, Caroli and Cachera gave a series of injections of posterior lobe of the hypophysis to patients with biliary disorders with a view to determine the functioning of the bladder; it happened that these injections were given to patients suffering also from bad attacks of migraine, and there was observed in a number of cases a rapid and lasting disappearance of headache and nausea. Following these observations, they gave this treatment to patients with various types of headache. The patients were affected with migrainoid pains associated with dyspeptic disorders other than gall bladder disease. Some were suffering from headache that had no relation with digestive disturbances: headache associated with seasonal "colds," or with migraine of menstruation. More than 20 patients were treated. Nearly all experienced relief within a few minutes. At first it was given subcutaneously; but the effect was the same when powder of the hypophysis was introduced into the nose. In studying this sedative action, the authors abandoned the theory that it was associated with emptying of the bladder and the drainage of bile. They considered the effect of the

hypophysis on the cerebral blood supply or on the pressure of the cerebrospinal fluid. The action of the hypophysis on the cerebral circulation resembled that of ergotamine tartrate, the therapeutic value of which in migraine is well known. Changes in the pressure of the cerebrospinal fluid are usually in the direction of hypertension.

The coefficient of luteinization, functional measure of the anterior lobe of the hypophysis (Le coefficient de lutéinisation, indice fonctionnel de la préhypophyse). Lipschütz, A., Compt. rend. Soc. de biol. **111:** 610. 1932.

In young rats from the same litter the number of corpora lutea formed after a dose of anterior lobe was found to be proportional to the size of the dose. To judge the relative number of corpora lutea, those seen in a single section of the gland are counted. The relative activity of different preparations can be expressed on this basis. By this method it appeared that hypophysis from infant female rats is forty times as strong as that from normal adult females and twice as strong as that from a castrated animal.—J. C. D.

Sex specific differences in the behavior of the anterior lobe of the hypophysis in the rat (Difference préhypophysaire du sexe chez le rat). Lipschütz, A., and G. Reyes, Compt. rend. Soc. de biol. **109:** 1330. 1932.

Evans and Simpson stated that the anterior lobe in the male rat is more active than that of the female. The question has been re-examined with special reference to the oestrogenic and luteinizing factor of the anterior lobe. The experiments reveal that equal quantities of male and female hypophysis give different results, even if animals of the same litter are compared. The hypophysis of the adult female contains less of the oestrogenic factor than the hypophysis of the adult male. If a greater quantity of anterior lobe of the adult female is injected, estrus is established, but there is no luteinization which may be absent even when as much as 72 mg. of hypophysis of the adult female is given, as against 21 mg. of male hypophysis given to an animal of the same litter.
—Authors' Abst.

The capacity for stimulating the formation of corpora lutea found in the hypophyses of young and old female rats (Sur la capacité lutéinisante de l'hypophyse de la Rate infantile et adults). Lipschütz, A. and G. Reyes, Compt. rend. Soc. de biol. **111:** 608. 1932.

Six young rats were injected with known amounts of anterior lobe from young female rats. Fifteen others received injections of material from adult females. The number of corpora lutea in the ovaries was estimated. The 1 to 1.5 mg. gland of the young rat had as much luteinizing action as the 6 mg. gland of the adult.—J. C. D.

Biological evaluation of the colloid of beef hypophysis (Biologische Auswertung des Kolloids der Rinder hypophyse). Noether, P., Klin. Wchnschr. **11:** 865. 1932. Abst., Chem. Absts. **26:** 5135.

Like the intermedin recently described by Zondek and Krohn, the colloid of beef hypophysis produces the spawning-time coloration in minnows within 20 minutes but does not initiate estrus in infantile rats, has no thyreotropic action in guinea pigs and does not affect ovulation in hens. Large quantities of colloid are found only in cows which have calved repeatedly.

Sexual activity of anterior pituitary lobe in female toads (Acción sexual del lóbulo anterior de la hipófisis en el sapo hembra). Novelli, A., Rev. Soc. argent. de biol. **8:** 454. 1932.

The percentage of females that ovulate when injected with suspensions of anterior lobe was found to be proportional to the dose, but with a given dose different percentages were observed in different batches of animals. It was found that ovulation can be provoked by anterior pituitary lobe after removal of liver, kidney, adrenals, pancreas, thyroids, digestive tract, fore-brain, pituitary and tuber cinereum. In Leptodactilus ocellatus (L) gir. alkaline extract of bovine anterior pituitary lobe did not produce ovulation. Removing the ovary one-half hour after injection of anterior pituitary lobe suspension and transplanting it into the peritoneum of a male or leaving it in saline did not result in ovulation. Ovaries submerged in suspension of anterior pituitary lobe did not ovulate.—J. T. L.

Hormone content of the anterior lobe of the human hypophysis. Ueno, A. and M. Murata, Tr. Jap. Path. Soc. **21**: 149. 1931. Abst., Chem. Absts. **26**: 6003.

The content of human hypophyseal anterior-lobe hormone was measured by the degree of appearance of puberty phenomena in mice after the injection of its aqueous extract. The hormone increases with age to the adult stage and begins to decrease during senility. It decreases in chronic diseases and carcinoma and increases during pregnancy. The hormone is present in man and woman in the same quantities.

Basal metabolism associated with E avitaminosis and the relation of anterior pituitary hormone (Der Grundstoffwechsel von Vitamin-E-frei ernährten Ratten und die Ergänzung des E-Vitamin-Mangels durch Hypophysenvorderlappenhormone). Verzár, F., A. v. Arvay and E. v. Kokas, Biochem. Ztschr. **240**: 19. 1931. Abst. Physiol. Absts. **17**: 527.

The change in appearance of the coat and the lowering in basal metabolism of rats suffering from E avitaminosis or castration are corrected both by vitamin E and by injection of anterior pituitary hormone. The hypothesis is advanced that lack of the vitamin induces decreased secretion of anterior pituitary hormone, which in turn is correlated with decreased secretion of testicular hormone.

Tumors in the pituitary area; the neurologic symptoms. Weisenburg, T. H., Arch. Ophth. **6**: 589. 1931. Abst., Arch. Neurol. & Psychiat. **27**: 1469.

The author discusses the functions of the pituitary area as indicated by experimental evidence. There is no doubt that the anterior lobe has two definite hormones, the first being concerned with the growth principle, and the second with the sex principle. While hyperpituitary symptoms are distinct from hypopituitary, they have this in common: they produce demonstrable regressive changes in the reproductive organs, for in both there is an inhibition of the ovarian cycle. The function of the posterior hypophysis is considered with that of the stalk, infundibulum and adjacent hypothalamic structures, for the reason that it is impossible to demonstrate clinically separate lesions of these separate structures. There is anatomic evidence of an interrelation between these parts; they have similar epithelial characteristics, and there is evidence that these cells represent the secretory principle which acts on all these inclusive structures. The infundibulum lobe is a downward extension of the diencephalon, and there is a connection between certain nuclei in the walls of the third ventricle and the posterior and middle portions of the hypophysis. These groups of anatomic entities probably house ancestral mechanisms, common to all species, which have to do not only with the vegetative functions, but also with primitive instincts, such as mating, satisfying hunger and thirst, restoration from fatigue by sleep, regulation of body temperature, self-protection by combat, etc. Furthermore, there is experimental and clinical evidence that the cerebral sympathetic centers are in the hypothalamus. Nonmedullated fibers have been traced to the spinal cord which connect with the abdominal and thoracic viscera, and there is evidence that some of these fibers connect with the anterior hypophysis itself. The clinical evidences of pathologic conditions in the region of the third ventricle are discussed. The author states that compression in the area of the third ventricle is most important, and is sometimes caused by pituitary tumors. The walls of the third ventricle consist of the optic thalami on either side. As the thalamus is a sensory organ, lesions in this area may cause so-called central pains. As a result of lesions in the vicinity of the third ventricle there are: disturbance in the sleep rhythm, usually hypersomnia; alterations in water metabolism, causing diabetes insipidus; disturbances in fat metabolism, and disturbances in growth and vegetative and emotional activities. If with hypersomnia there occur diabetes insipidus, adiposity and genital dystrophy, a lesion of the hypothalamic region should be suspected. On the other hand, primary hypophyseal tumors, not projecting into the third ventricle, may cause apathy and lethargy from lowered metabolism. Disturbances of the menstrual cycle in women and of the libido in men is the most common symptom in a pathologic condition of the anterior lobe. Headache is an early symptom and is usually frontal. Slight fatigability is common. Hypoplasia of the genital organs occurs in childhood, and an absence of secondary sexual characteristics in a person past the age of puberty. With the general inhibition of growth there are segmental deposits of fat in the abdomen,

pelvis, shoulders, neck and breasts, the distal extremities appearing normal. In the third part of the paper the author discusses pituitary tumors. They may be divided into intrasellar and extrasellar. The intrasellar tumors are most often adenomas, which have origin in the glandular cells within the anterior lobe of the pituitary body. Histopathologically, they are: the chromophilic adenomas associated commonly with a clinical picture of acromegaly; the basophilic adenomas, a rare type, which are probably related to reproductive processes; the chromophobic adenomas associated clinically with the hypopituitary syndromes. A second type of intrasellar tumor is that of Rathke's pouch. These tumors are composed of epithelial cells often stratified and presenting rosettes into which cilia project from the cells of the buccal mucosa. The suprasellar tumors are tabulated as: adenomas, meningiomas, tumors of the craniopharyngeal duct, gliomas of the optic chiasm and aneurysms. These tumors give rise to the "chiasmal syndrome," primary optic atrophy, bitemporal hemianopia and a normal or relatively normal sella turcica, in contradistinction to the marked enlarged and ballooned-out sella turcica, in primary pituitary tumors. A table compares the pathology and symptomatology of all the various types found. The meningiomas occur in middle age and produce endocrine disorders rather late. The adenomas escaping through the diaphragm cause mild hypopituitary signs, and are of more rapid course than the meningiomas. The craniopharyngeal duct tumors and adamantinomas, which are always suprasellar and often calcified, frequently cause secondary pituitary, hypothalamic symptoms and endocrine disturbances. Gliomas arise from the chiasm or the adjacent wall of the third ventricle and occur in young persons. Aneurysms are also included in this group of suprasellar lesions. In a section on differential diagnosis it is pointed out that tumors of the pituitary may give rise to symptoms lesions elsewhere by direct extension into distant parts; or by extension through the ventricle system and through the aqueduct of Sylvius, causing midbrain symptoms; instead of a direct extension of the tumor, a generalized internal hydrocephalus may be produced, with dilatation of the lateral, third and fourth ventricles and attendant phenomena. On the other hand, tumors of the cerebellum frequently cause symptoms of dyspituitarism because of a secondary internal hydrocephalus, dilatation of the lateral and third ventricles and direct pressure on the pituitary region. In differential diagnosis, an adequate history of the progress of the symptoms is most important, for when lesions encroach on the pituitary area the corresponding symptoms appear late. These have been found in cases of generalized internal hydrocephalus in which a diagnosis could not be made before a postmortem examination.—Abst. Abbreviated.

The effect of hypophysectomy on the survival of spermatozoa in the male rat. White, W. E., Anat Rec. **54**: 253. 1932.

Sperm motility determinations were made in three series of hypophysectomized rats. The first series was hypophysectomized only. In addition to hypophysectomy, the second series was bilaterally vasa-efferentia ligated, and the third was bilaterally castrated. The motility readings were compared with non-hypophysectomized rats, one series of which was bilaterally castrated, the second unilaterally castrated, and the third vasa-efferentia ligated. Readings were taken from the head and tail of the epididymis, from the ductus deferens, and in the non-castrated animals from the testes also. Motility persisted for 21 days in the hypophysectomized rats, which is much shorter than after unilateral castration (45 days), or vasa-efferentia ligation (42 days). Hypophysectomy thus markedly shortens sperm survival in the male rat. Vasa-efferentia ligation does not decrease the survival of sperm in hypophysectomized animals, indicating that there is no postoperative contribution of sperm from the testes. Castration does not decrease the survival of sperm in hypophysectomized animals, indicating that no internal secretion beneficial to sperm survival is elaborated by the testes after the removal of the pituitary. The pituitary does not supply any substance which is directly beneficial to sperm survival as demonstrated by the fact that the period of survival is no greater in castrated non-hypophysectomized rats than it is in the hypophysectomized individuals (21 days in each). —Author's Abst.

Ovarian responses to prolan and anterior pituitary extract in hypophysectomized rabbits with particular reference to ovulation. White, W. E. and S. L. Leonard, Am. J. Physiol. **104**: 44. 1933.

In experiments on 3 to 6 rabbits it was found to take one-sixth to one-third more of a minimal ovulating dose of an anterior lobe extract and one-half more

of a minimal ovulating dose of prolan to induce ovulation than in rabbits hypophysectomized in heat, hence it appeared that the injected hormone producing ovulation was acting independently of the intact hypophysis. The corpora lutea that formed from such methods of stimulation in the hypophysectomized rabbit were similar to those previously reported by Smith and White. These smaller corpora were quite capable, however, of producing sufficient corpus luteum hormone to form, histologically, a progestational endometrium in the uterus. In order to induce follicular stimulation in the ovaries of hypophysectomized rabbits, a great increase of prolan over gonadotropic pituitary preparations was needed.—R. G. H.

Anterior lobe pituitary hormone and amenorrhea (Hypophysenvorderlappenhormone und Amenorrhöe). Wirz, P., Ztschr. f. Geburtsh. u. Gynäk. **104:** 293. 1933. Abst., J. A. M. A. **100:** 1215.

Wirz, in his study of the relation of the anterior pituitary hormone to functional amenorrhea, quotes Zondek's statment that the pituitary gland secretes sex controlling hormones at all ages, and he investigates the status of these hormones in the course of amenorrhea. According to Zondek, prognosis in functional amenorrhea is poor if a five-time concentration of urine reveals the presence of the follicle-maturing hormone. Utilizing this functional method, the author examined the urine of women with an irregular cycle, and of women who had ceased menstruating for some time. The author's experiments aimed at the solution of the following questions: (1) The fate of the anterior pituitary hormone before sexual maturity and the question of its being excreted in the urine. (2) The fate of the hormone during amenorrhea of lactation. (3) The fate of the sex controlling pituitary hormones in amenorrheas of ovarian origin at sexual maturity. The author found that the pituitary glands of fetuses, of the new-born and of children under five years contained the follicle-ripening hormone A but not the luteinizing hormone B. The entire gland before the first year hardly contained a single mouse unit. Hormone A was excreted in small amounts in the urine of children. The author supposes that hormone B is not secreted until shortly before puberty. The increased secretion of hormone A, together with the appearance of hormone B at the time of sexual maturation, are responsible for the establishment of the ovarian cycle. He failed to find the sex hormones in the pituitary glands of parturient women shortly after delivery. After a full term pregnancy, hormone A appears in the urine from two to three weeks, post partum, while hormone B appears from five to six weeks post partum, the latter fact coinciding with the onset of the first ovulation. This explains the frequent onset of menstruation six weeks post partum. The failure to menstruate in a lactating woman is accompanied by an increased excretion of the hormone in the urine. This type of amenorrhea is of ovarian origin, since the pituitary hormone is secreted at this period as well. With regard to amenorrhea of ovarian origin in nongravid women, it was found that the prognosis was poor if the hormone was present in the amount of 110 mouse units for each liter of urine. In such cases, folliculin (ovarian hormone) could not be demonstrated. The question of whether the increase of hormone A in these cases is due to increased production in the pituitary or to the failure on the part of the ovary to utilize it has not been answered. The author agrees with Zondek that the presence of 110 mouse units in a liter of urine in cases of amenorrhea signifies a total suspension of ovarian function. It is obvious that administration of anterior lobe pituitary extracts in such cases is futile.

Hormone of pars intermedia of the pituitary gland (Hormon der Zwischenlappens der Hypophyse [Intermedin]. III. Zur Chemie, Darstellung und Biologie des Intermedins). Zondek, B. and H. Krohn, Klin. Wchnschr. **11:** 1293. 1932. Abst., Physiol. Absts. **18:** 60.

To prepare intermedin free from vaso-pressin and oxytocin, the acetone-dried glands are extracted thrice with boiling 0.25% acetic acid. The solution is evaporated to dryness and extracted three times with hot absolute alcohol. The extract is evaporated and the residue, which still contains traces of oxytocin and vaso-pressin, is taken up in water, filtered after 24 hours, and treated with NaOH (1%). After 24 hours the vaso-pressin and oxytocin are destroyed. The solution is now neutralized with HCl. Intermedin has been obtained thus with one unit of activity in one gamma. It is soluble in water, protein free, not destroyed by boiling, and fully adsorbed by charcoal and kaolin. It is more stable to NaOH than vaso-pressin and oxytocin. Its biological action is exerted

solely on the melanophores. After injection of 65,000 units into a rabbit over a period of three weeks no intermedin could be detected in the urine, and only traces were found in the blood three hours after the last injection. It is thus quickly destroyed. It has no action on plain muscle or on the blood sugar.

Prolan and growth of tumors; inhibiting influence of prolan on growth of tumors in white mice (Prolan und tumorwachstum. Der hemmende Einfluss des Prolans auf das Impfcarcinom der weissen Maus). Zondek, H., B. Zondek and W. Hartoch, Klin. Wchnschr. **11**: 1785. 1932. Abst., J. A. M. A. **99**: 2299.

The authors report studies based on the clinical observation that in acromegaly the growth hormone, which in this conditioin is presumably produced in large quantities, inhibits follicle maturation. Thus it seemed reasonable to examine whether, on the other hand, the hypophyseal hormone effecting follicle maturation would influence growth process, particularly tumor growth. It may be significant that patients with tumor eliminate in the urine considerable quantities of the hormone of the anterior lobe of the hypophysis. Tests were made on 1,019 sexually mature white mice. The investigations revealed that by means of prolan (containing both the follicle maturation hormone and the luteinization hormone) it is possible to inhibit greatly the growth of inoculated tumors, while in animals not treated with prolan the tumors weighed about 1.65 gm. after 23 days; in animals treated with prolan the tumors weighed only 0.2 gm. The authors further describe tests in which it was determined that the inhibiting influence of prolan is not exerted by the inorganic substances which it contains. In another series of animals it could be demonstrated that the administration of prolan reduces the growth energy of a tumor to such an extent that in the second animal passage the tumor grows only slightly or not at all.

Insulin sensitiveness and the carotid sinus (Über Insulinempfindlichkeit und Sinus Caroticus). Casas, J. and K. Hinsberg, Klin. Wchnschr. **11**: 641. 1932. Abst., Physiol. Absts. **17**: 517.

The carotid sinus was denervated in rabbits in two operations four to five days apart. The sensitiveness to insulin was then determined by blood-sugar analyses. It was found to be greater than before the operation; the initial hyperglycemia and hypoglycemia that followed were both more marked.

Use of insulin in treatment of pulmonary tuberculosis. Ellman, P., Brit. J. Tuberc. **26**: 187. 1932. Abst., J. A. M. A. **100**: 76.

The author outlines the value of insulin as a therapeutic measure in certain selected cases of phthisis to restore normal appetite and combat loss of weight and resistance. It is especially indicated in afebrile, inactive cases of phthisis, when failure to gain weight in a previously robust person persists despite the usual therapeutic measures. No treatment should be undertaken without clinical, radiologic and bacteriologic control. Observations of weight, pulse, blood pressure and temperature should be made when using insulin. Insulin is contraindicated in cases of fever, active disease, hemoptysis, marked hypotension and severe reactions following injections. The author commences treatment with a hypodermic injection of 5 units of insulin twenty minutes before the principal meal. To avoid any risk of hypoglycemia patients should be advised to drink a glass of milk, or take dextrose, and to carry a few lumps of sugar with them, and should they develop any symptoms of hypoglycemia, such as general weakness, listlessness, shakiness, palpitating nervousness, giddiness or sweating, to take a lump of sugar. The injection of 5 units of insulin should be continued daily for the first week. This is increased by 5 units weekly until 30 units are taken as a daily dose for from one to three weeks. The author never exceeds the 30-unit dose.

Latent tolerance in diabetes mellitus. Gibson, R. B., Am. J. Physiol. **101**: 41. 1932.

Continuing previously reported observations (1928), a number of mild diabetics have been restored promptly to a normal carbohydrate tolerance when a Woodyatt type diet on which they were controlled without insulin was changed to a diet of protein 46 grams, carbohydrate 204 grams or more, and fat 100 grams with insulin in progressively decreasing dosage. More severe cases show

a partial response; they reach a normal tolerance but do not maintain this, or they improve as indicated by prompt insulin reduction when returned to routine management and even are able to dispense with insulin. Certain patients, however, do not respond to this procedure. One patient who has been routinely managed by diet and later both diet and insulin recently developed repeated autogenous hypoglycemic attacks following two separated periods of tolerance stimulation (each time after recovery from diabetic coma) with subsequent stabilization of the blood sugar within normal limits on a general diet. These results confirm the idea earlier expressed that a dormant rather than a functionally inadequate mechanism may obtain in diabetes and that it may be stimulated to activity under appropriate conditions.—Author's Abst.

The relations between insulin and adrenaline in humans (Ueber die Beziehungen zwischen Insulin und Adrenalin im menschlichen Organismus). Kugelmann, B., Klin. Wchnschr. **10:** 59. 1931. Abst., J. de path. et de path. gen. **30:** 180.

The author injected 30 units of insulin early in the morning and found after 30 minutes that the blood sugar had reached a minimal value of 48 mg. per 100 gr. During this decrease there was an increase of systolic pressure which started when the blood sugar level reached 60 mg. This increased pressure did not occur unless the glycemia curve reached 60 mg. At the same time the diastolic pressure decreased. This behavior of the blood pressure is regarded as an adrenaline symptom. In hypertension patients when sugar is administered at the same time insulin is injected there results a lowered systolic pressure independent of glycemic changes. Insulin also causes a decrease in the total number of leucocytes which increase again when the pressure begins to rise. At the same time the proportion of lymphocytes reaches a high value, sometimes even 60%. In patients with enlarged livers which decrease under adrenaline injections it is found that as soon as the insulin causes an increase in pressure the size of the liver decreases. Thus in hypoglycemia there is an abnormal amount of adrenaline in the blood just as if hypoglycemia could mobilize the adrenaline depots. The organism thus prepares for too great a decrease in the blood sugar.—Translated by J. Gagnon.

The dynamics of internal secretions. I. Methods (Inkretionsdynamik. I. Methodische Angaben). London, E. S., Pflüger's Arch. f. d. ges. Physiol. **228:** 531. 1931. Abst., Physiol. Absts. **17:** 439.

Methods are described by which the outflow from small veins (pancreaticoduodenal, suprarenal) can be collected. Small quantities of insulin and adrenaline are biologically estimated by intraperitoneal injection into white mice, the effect on the blood sugar being determined.

The dynamics of internal secretions. III. Internal and external secretions (Inkretionsdynamik. III. Sekretion und Inkretion). London, E. S., Pflüger's Arch. f. d. ges. Physiol. **228:** 542. 1931. Abst., Physiol. Absts. **17:** 439.

There is no relation between the internal and external secretions of the pancreas. The effects of various foods on the secretion of pancreatic juice and of insulin were determined; the two secretions attain a maximum at widely different periods. After the ingestion of bread there was a marked increase in the secretion of insulin; this was due to the formation and absorption of sugar. There is an antagonism between the secretions of insulin and of adrenaline.

Insulin and liver fat (Inselorgan und Fettstoffwechsel der Leber). Löw, A. and A. Krčma, Klin. Wchnschr. **11:** 584. 1932. Abst., Physiol. Absts. **17:** 518.

Rats were given a fat-rich meal after a previous 24-hour fast. After various intervals of time (from one hour to 2½ days) they were killed and the liver fat, total liver carbohydrate, blood fat, and blood sugar determined. The results were compared with those from rats treated in the same way, but receiving insulin (0.2 to 0.4 unit) ½ hour before the fat-rich meal. The experiments show that the fatty infiltration of the liver in the control animals is prevented by the administration of insulin. Insulin likewise diminished the carbohydrate content of the liver, the blood sugar, and the blood fat. In the estimations of liver fat a light petroleum extract (chiefly neutral fat) and an alcoholic extract (chiefly lipins) were made. The fatty changes observed under insulin were principally in the former.

Variations in free and combined sugar in diabetics following ingestion of glucose with or without insulin (Les variations du sucre libre et protéidique chez les diabétiques a la suite d'ingestion de glucose, avec ou sans insuline). Rathery, F. and I. Cosmulesco, Compt. rend. Soc. de biol. **110:** 1264. 1932.

Fourteen diabetics received glucose alone and later glucose and insulin. The free sugar increased markedly in the first instance, not so markedly, though definitely, in the second. The bound sugar was not definitely influenced.

—J. C. D.

Action of pain stimuli on the internal secretions of the adrenals and pancreas and the blood sugar. Shcherbakov, S. A., V. S. Zimnitzkii, A. A. Vishnevskii and Z. A. Zatornitzkaya, Russ. Physiol. J. **14:** 152. 1931. Abst., Chem. Absts. **26:** 5330.

Faradic stimulation of the ischiadicus in cats and dogs causes an increase in blood sugar only when the adrenals are intact. When the latter are excluded a decrease in blood sugar is observed. Blood taken from the vein leaving the adrenal immediately after the application of pain stimulus increases the blood-sugar content when injected into the second animal. When the pancreas is removed the pain stimulus causes a sharp increase in blood sugar of long duration. On removal of both glands the pain stimulus does not affect the blood sugar.

Studies on the influence of various glands of internal secretions on the gas exchange in animals suffering from B avitaminoses. II. The influence of insulin (Studien über den Einfluss der verschiedenen innersekretorischen Drüsen auf den Gaswechsel der B-avitaminösen Tiere. II. Ueber den Einfluss des Insulins). Shinobe, S., Folia endocrinol. japon. **7:** 40. 1931. Abst., Chem. Absts. **26:** 5326.

Repeated insulin injections somewhat prolonged the life of animals fed on a diet lacking in vitamin B. The appearance of motor paralysis was unchanged. The oxygen consumption of these animals was at first increased by the insulin, then, in contrast to the controls, checked. The respiratory quotient remained unchanged.

Studies in parathyroid physiology; effect of phosphate ingestion in clinical hyperparathyroidism. Albright, F., W. Bauer, D. Claflin and J. R. Cockrill, J. Clin. Investigation, **11:** 411. 1932.

Three cases of clinical hyperparathyroidism were treated by the ingestion of phosphate with beneficial results. The metabolic sequelae of such treatment were: (1) almost complete absorption of phosphates into the blood stream; (2) rapid excretion of the absorbed phosphates by the kidney; (3) a rise of the previously low serum phosphorus; (4) a fall of the previously elevated serum calcium; (5) a rise at first of the Ca x P product in the serum, and (6) a fall of the urinary calcium excretion. The net result was an increase in the calcium and phosphorus balances and a return of the serum calcium and phosphorus in the direction of normal. The rapidity with which the absorbed phosphorus was excreted in the urine and the resistance which the low serum phosphorus exhibited to being raised suggested that the threshold for phosphorus excretion into the urine is lowered in hyperparathyroidism. This is regarded as the most fundamental change in the calcium and phosphorus metabolism in this condition. There were emphasized two clinical dangers of phosphate ingestion in hyperparathyroidism: (1) precipitation of the state of parathyroid hormone overdosage with death from uremia, with calcium deposits in the lungs, mucosa of the stomach, thyroid gland and kidney parenchyma and (2) danger of producing bilateral phosphate stones in the kidney.—W. Bauer.

Estimation of parathyroid hormone. Dyer, F. J., J. Physiol. **75:** 13. 1932. Abst., Chem. Absts. **26:** 5593.

The parathyroid hormone can be assayed by determining the dose which must be injected into a rat to produce a rise in urinary Ca in 24 hours equal to the rise produced by a standard dose.

The influence of calcium salts and parathyroid extract upon the energy liberation and efficiency of the heart. Peter, H., C. E. Rea and M. B. Visscher, Proc. Am. Physiol. Soc. P. 79. 1933.

The addition of calcium salts or parathyroid extract to the blood of the heart-lung preparation causes a significant decrease in the diastolic volume of the ventricles at constant venous pressure and with minimal changes in the heart rate. The stroke output increases and therefore the work per beat increases. The oxygen utilization of the heart has been measured by placing the preparation in a suitable glass and bakelite chamber, immersing the whole in a large water bath at constant temperature. The oxygen removal was determined with a closed circuit respiration system. It has been found that the energy liberated per beat at a constant fiber length increases with addition of calcium salts. In this respect the action resembles that of adrenaline. However, calcium addition causes the heart muscle to convert a larger proportion of the energy released to useful work, which is in contrast to the effect of adrenaline.—Authors' Abst.

The effect of parathyroid hormone and of irradiated ergosterol on calcium and phosphorus metabolism in the rat. Pugsley, L. I., J. Physiol. **76**: 315. 1932.

Injection of as little as 5 units of parathyroid extract daily in the rat will increase serum calcium and increase the excretion of urine and fecal calcium and of urine phosphorus. The increased urine calcium excretion is maintained only a few days, suggesting immunity. Injection of 20,000 to 50,000 units daily of irradiated ergosterol causes increased urine calcium excretion but decreases fecal calcium and phosphorus. This occurs in rats already immune to parathyroid extract. The author concludes that any stimulation of parathyroid tissue by large doses of irradiated ergosterol is an unimportant part of its total action.
—C. I. R.

Further studies on the physiological action of irradiated ergosterol. Reed, C. I., Proc. Am. Physiol. Soc. P. 83. 1933.

It has been shown previously that irradiated ergosterol, when administered in large doses to normal dogs will effect a pronounced increase in the rate of oxygen consumption. This does not follow from the administration of excessive amounts of parathormone. This indicates that, at least, a part of the effect of irradiated ergosterol administration is independent of the parathyroids. In dogs on a standard diet but fasting 24 hours balance experiments have consistently failed to show any pronounced constant effect on nitrogen consumption. Apparently the fundamental effect of irradiated ergosterol on metabolism is modified in some way by the consumption of a normal diet.—Author's Abst.

The effect on the body temperature of animals of injection of an extract of parathyroid glands. Robinson, M. H. B. and J. H. Thompson, J. Physiol. **77**: 26P. 1933.

A parathyroid extract that is free from the calcium raising factor (cf. J. Physiol. **76**: 303. 1932) when injected into 12 rabbits in five weeks caused a decrease in rectal temperature from 100.7-101.5° F. to 99.1-100.1°. Comparable results were obtained in rats (number not stated).—R. G. H.

Action of parathyroid hormone on the epiphyseal junction of the young rat. Selye, H., Arch. Path. **14**: 60. 1932. Abst., Chem. Absts. **26**: 5143.

Young rats are more resistant to an overdosage of parathyroid extract than adult rats. Even when fatal doses of parathormone are administered to young rats, extensive metastatic calcification does not occur, as is invariably the rule in adults. On the other hand, the bony system of young rats is readily and seriously damaged by large doses of parathormone and the changes so produced are most striking in the region of the epiphyseal junction in the so-called growth zones. There the changes are suggestive of severe rickets. The theory that Viosterol acts through the medium of the parathyroid glands is not confirmed by these experiments, as the disease produced by hyperparathyroidism in young rats described in this paper differs markedly from that produced under the same conditions by the so-called "hypervitaminosis D."

Scleroderma and its causation (Die Sklerodermie und ihre Entstehungsweise). Selye, H., Virchows Arch. f. path. Anat. **286:** 91. 1932.

Injections of large doses of parathyroid hormone into suckling rats led to a skin disease closely simulating scleroderma. The possible rôle of the parathyroid in the etiology of scleroderma is discussed.—Author's Abst.

A case of homotransplant of parathyroid for tetany. Tainter, F. J., Proc. Soc. Western Surgical Assoc., Abstract J. A. M. A. **100:** 286. 1933.

Mrs. T., aged 42, was operated on for goiter twice nearly five years ago. Immediately following the second operation tetany developed. She had tingling sensations in the extremities, and sensations of pricking as of needles and pins in the fingers. These were accompanied by spasms of the hands and the feet, distension and hardness of the abdomen, with a general neuromuscular irritability with marked spasms. Chvostek's sign was present. There was mental irritability and muscular weakness with loss of weight. Erb's sign was positive. as well as Trousseau's sign, and was easily reproduced at will, by slight pressure on the large nerve trunks. There was evidence of hypocalcemia. The blood serum calcium was always about 50% below normal. Three months after these symptoms developed, the patient went to competent internists, who treated her for tetany. Under this treatment she was fairly comfortable but required several daily injections of calcium chloride, parathyroid extract and lactated calcium. April 18, 1931, two parathyroid glands were removed from her mother, who was 67 years of age and whose blood did not match with that of her daughter's. The removed parathyroids were placed into the sheath of the rectus muscle of the patient. About eight months after the operation, calcium and parathyroid extract were gradually decreased until about the middle of July, 1932, since which time she has not required any treatment for tetany. She has gained 48 pounds (22 Kg.), and the blood serum calcium is 8.5 mg. per hundred cubic centimeters of blood. Her mother is in perfect health, and she has not shown at any time the effect of the loss of some of the parathyroid glands. What the ultimate results will be is still a question. The case, in many respects, differs from any heretofore reported.

On the mechanism of parathyroid hormone action. Thomson, D. L. and L. I. Pugsley, Am. J. Physiol. **102:** 350. 1932.

The intravenous injection of parathyroid extract in two dogs led to a rise in serum calcium unaccompanied by any fall in plasma phosphate; marked lowering of phosphate by injection of glucose and insulin elevated the serum calcium only to a trivial extent. The characteristic time-relations of the hypercalcemic response to parathyroid extract were not altered by the simultaneous injection of calcium salts. These findings indicate that the parathyroid hormone does not act primarily by depressing the plasma phosphate nor by increasing the solvent power of plasma for calcium compounds, and the view that it directly stimulates the osteoclasts to mobilize calcium from the bones is preferred.—Authors' Abst.

A case of calcification of the pineal gland associated with other endocrine disturbances (Über einen Fall von multipler Blutdrüsenerkrankung mit Beteiligung der Zirbeldrüse). Taubenhaus, M., Endokrinologie, **11:** 324. 1932.

A case of diabetes mellitus and calcification of the pineal gland in an 18-year-old boy of eunuchoid type is reported.—R. A. Phillips.

Internal secretion of pineal gland and the therapeutic use of its extracts. Wíslánski, K., Ginek. polska. **11:** 396. 1932. Abst., Surg., Gynec. & Obst. **56:** 358.

The author performed experiments on animals, using non-toxic, sterile 1% aqueous extracts of the pineal gland and a preparation called "epiphysan." The basal metabolism was increased in the animal as well as in man. On the other hand, the specific dynamic metabolism varied little after the administration of protein. The action of the extract upon the non-pregnant uterus and bowel of the guinea pig resulted in a decrease in the tone of the smooth muscle. Its

action on the pregnant uterus was entirely different as it stimulated uterine contractions. Injections of from 0.5 to 1.5 cc. of a 1% aqueous extract of the pineal gland into young rabbits of both sexes produced a retardation of growth and a decrease in the size of the organs. The thyroid glands of these animals were much smaller than those of the control animals and contained less colloid material. In the ovary, degeneration of the follicles was observed. In the uterus, the muscle fibers disappeared and there was a proliferation of the stroma. In the testicles, degeneration of the cells and a decrease in the number of spermatozoa were found. Similar, though less marked, changes were noted in the mature animal. In the mature animals the uterus enlarged as the result of proliferation of the connective tissue and stroma under the influence of the pineal gland extract. The endometrium showed a proliferation of the connective tissue. All of the experimental animals, both males and females, were sterile for one and one-half years. On the basis of the results of his experiments the author began to treat dysmenorrhoea due to congenital hypoplasia of the uterus with extract of the pineal gland. The result was the establishment of normal, painless menstruation. The extract has been employed successfully also in the treatment of painful urination, marked contraction of the non-pregnant uterus, spastic conditions of the colon, and all conditions with increased spasticity of the smooth muscle. In cases of hypertension the extract produces a definite drop in the blood pressure and is antagonistic to the extract of the posterior lobe of the pituitary gland, which increases the tone of the smooth muscle. The nervous phenomena following the removal of the uterus and ovaries disappear in most cases after the administration of pineal gland extract. The author states that he used the extract very successfully in the case of a woman forty-two years old who complained of severe postoperative nervous symptoms and eczema of the lower extremities. By means of the Aschheim-Zondek test he determined that the curative effect of the extract on the eczema was due to its direct action on the metabolism and was not brought about indirectly by the anterior lobe of the pituitary gland. From these observations and those of others the author concludes that the extract of the pineal gland affects all of the other endocrine organs and especially the genital organs. Its action is variable and depends considerably upon the sex of the patient. Even its action on the genital organs is variable as there is an inhibiting action in addition to a stimulating action. Therefore we must conclude that the function of the pineal gland depends upon factors as yet unknown which influence the character of its action.—Abst. Abbreviated.

The antagonism between thymus and suprarenal medulla (Esperienze sul cuore isolato in relazione all-antagonismo fra timo e midollare surrenale). Cartolari, C., Arch. internat. de pharmacodyn. et de thérapie, **41**: 313. 1931. Abst., Chem. Absts. **26**: 6000.

Extracts of the thymus exert a depressor action on the isolated heart of the frog and toad. This action is antagonized by adrenaline. Thymus extract administered after adrenaline causes the disappearance of the adrenaline effect.

The diagnostic value of phagocytosis in thyroid disease (Über die Verwertbarkeit der Phagozytose in der Diagnostik der Schilddrüsenerkrankungen). Aeschlimann, H., Endokrinologie, **12**: 101. 1933.

The author describes technical procedures for the study of the phagocytosis of starch granules. This technique is modified by the addition of blood plasma from patients with various diseases as well as normal individuals. He describes a daily fluctuation in the normal and gives a fairly extensive tabulation of the percentage of variation in patients with such infections as tuberculosis, empyema, arthritis, endocarditis, erysipelas and the like. Especially does he study the effect of the blood plasma in patients with hypothyroidism and hyperthyroidism on the phagocytosis of starch. He extends this study to the effect of the administration of iodin and of operation. The conclusion drawn from his experimental work is that the study of an individual patient in response to the effect of his serum on phagocytes is hardly accurate enough to warrant the use of this procedure as an important diagnostic instrument as used in the diagnosis of toxic goiter.—N. A. Womack.

Studies on the physiology of glands. Further experiments on the relationship between spleen and thyroid and iron metabolism (Beiträge zur Physiologie der Drüsen. Fortgesetzte Untersuchungen über die Beziehungen von Milz und Schilddrüse zum Eisenstoffwechsel). Asher, L. and H. Tschumi, Biochem. Ztschr. **251**: 418. 1932. Abst., Chem. Absts. **26**: 5635.

Hyperthyroidization produced in rabbits by thyroxine injections causes a marked rise in the iron excretion. Splenectomy is followed by a lowering of iron elimination but even in the splenectomized animal the injection of thyroxine produces an increased excretion of iron.

Sporadic goiter on genotypical basis and relation to other thyroid disorders. Bing, J., Ugesk. f. laeger. **94**: 705. 1932. Abst., J. A. M. A. **99**: 1124.

Bing presents a family with nine certain and one doubtful case of sporadic goiter on a genotypical basis. He believes that the heredity can be explained as due to a dominant factor limited to the female sex and that there is no connection between the inheritance of goiter and the blood type. Of 561 cases of sporadic goiter familial disposition was assigned in 17.1%, and a large series of cases of exophthalmic goiter and a smaller one of cases of sporadic goiter gave similar figures. A family with cases of sporadic goiter and primary exophthalmic goiter, a second with sporadic goiter and myxedema, and a third with sporadic goiter, exophthalmic goiter and myxedema are reported.

Congestive heart failure and angina pectoris; the therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity. Blumgart, H. L., S. A. Levine and D. D. Berlin, Arch. Int. Med. **51**: 866. 1933.

Reasons are given for believing that patients with a normal metabolism who suffer from congestive heart failure or angina pectoris might show striking improvement if the metabolic rate were significantly lowered. The hearts of such people might be unable to supply enough blood for the ordinary demands of a normal metabolic rate, but nevertheless might be able to supply enough blood for a reduced metabolic rate. The present communication reports the results of producing a subnormal metabolic rate by thyroidectomy on three patients who were suffering from severe congestive heart failure but who showed no evidences of disturbed thyroid function, and on one patient with angina pectoris with a slight elevation of metabolism but with a normal gland. In the patients studied the signs and symptoms of circulatory insufficiency and of angina pectoris had persisted for a considerable time in spite of all known medical procedures. The clinical condition of each patient was accurately studied during a long control period in order that any change following thyroidectomy could be attributed confidently to the effect of the procedure. In two of the three patients with severe congestive heart failure, subtotal thyroidectomy caused a fall in the metabolic rate which reached its maximum about three weeks after operation. Clinical improvement paralleled the lowered metabolism and was evidenced by the disappearance of edema, the increased vital capacity of the lungs and the ability to be up and about the ward without discomfort. During the next few weeks, the basal metabolic rates in these two patients again rose toward the preoperative normal level, and their clinical conditions became less favorable. One of these patients continued for an additional month to show a somewhat lessened metabolic rate than before operation, and his clinical condition, while not so good as that three weeks following operation, was definitely better than before operation. The patient with angina pectoris has shown no recurrence of the attacks of angina pectoris since subtotal thyroidectomy, although he has returned to work and active life. This is in contrast to his condition before operation, when attacks of angina pectoris occurred even while he was at rest. In one patient with congestive heart failure all thyroid tissue was removed, the parathyroid glands being spared. This patient has maintained his conspicuous clinical improvement and the metabolic rate has remained persistently lowered for more than six weeks. Further studies are being made in order to appraise the value of thyroidectomy and the effect of roentgen irradiation more accurately. The application of this procedure to other conditions in which a lowering of the metabolic rate may prove beneficial is also being studied. In the meantime the procedure should be employed only in carefully selected cases in which all known therapeutic measures have proved ineffectual.—Authors' Summary.

The comparative effects upon metabolism of intravenously injected tyrosine, diiodotyrosine, diiodothyronine and thyroxine. Canzanelli, A. and D. Rapport, Am. J. Physiol. **103**: 279. 1933.

Tyrosine, diiodotyrosine, diiodothyronine and thyroxine were administered to 3 dogs by intravenous injection, and the effects on the gaseous exchange studied. The maximum rise due to 1.0 gm. of tyrosine was 10% of the total metabolism, the effect lasting about 10 hours, the average total increase being about 220 Cals. per gram of tyrosine per kilo of animal. Diiodotyrosine produced about 7.5 times as much effect as did tyrosine; diiodothyronine about 15 times that of diiodotyrosine; and thyroxine about 17 times that of diiodothyronine. Generally speaking, the greater the total increase, the more prolonged the effect. The effect of all of the substances but thyroxine began almost at once (not later than ½ to 1 hour after administration); in the case of thyroxine an appreciable effect was delayed 4 to 5 hours. Though the ratio of the effects of thyroxine and tyrosine is about 2000 to 1, the data would indicate a step-like progression in stimulating influence as iodine and the phenyl radical are added to the tyrosine molecule in certain positions. The significance of this is not at present clear.—R. G. H.

The heart in hyperthyroidism; an electrocardiograph study (Le coeur chez les hyperthyroidiens. Etude electrocardiographique). Castex, M. R., M. Schteingart and A. Battro, Rev. franç. d'endocrinol. **9**: 185. 1931.

Although there is no consistently characteristic modification due to hyperthyroidism, the following conditions are more often met; modification of (a) auricular complex, (b) ventricular complex (partial), (c) total of both. The heart of the hyperthyroid is more sensitive to infection than the normal heart.
—B. C.

Acid-base equilibrium in thyroid disease (L'équilibre acido-basique dans les maladies de la glande thyroïde). Coelho, E., Rev. franç. d'endocrinol. **9**: 376. 1931.

In hypothyroidism and myxoedema the alkali reserve variations were found to be similar to those of hyperthyroidism, hence this datum is not of diagnostic value.—B. C.

Effects of certain extracts on basal metabolism of guinea pigs. Cole, W. H. and N. A. Womack, Proc. Soc. Exper. Biol. & Med. **30**: 83. 1932.

An increase in the basal metabolic rates of guinea pigs was produced when to the animals' diet was added a petroleum ether extract of the urine of human beings with toxic goiter. The greatest increase found was 18% over a period of 3 weeks. Animals given thyroid substance in addition to the ether extract of urine from toxic goiter patients showed a greater increase in metabolic rate than those given the thyroid substance alone. Similar extracts of urine from normal persons tended to counteract the effect of thyroid substance on the metabolism.—M. O. L.

Studies in the physiology of vitamins; the effect of experimentally-induced hyperthyroidism on the vitamin B requirement of pigeons. Cowgill, G. R. and M. L. Palmier, Am. J. Physiol. **105**: 146. 1933.

In a group of 12 pigeons subsisting on a diet adequate except with respect to the vitamin B complex, the minimal amounts of a yeast vitamin B concentrate required daily for maintenance of a practically constant body weight were determined. Hyperthyroidism was then induced experimentally in each of the birds by the daily administration of 100 mgm. of desiccated thyroid tissue and the amount of vitamin B concentrate required for body weight maintenance was again determined. In every case the vitamin B requirement proved to be greater in hyperthyroidism than under "normal" conditions. It is concluded that in the dog there is some relation between the amount of vitamin B required for maintenance of body weight and the metabolism of the organism.
—Authors' Summary.

The iodine-x-ray treatment of Basedow's disease (Die Jod-Röntgen-Therapie der Basedowschen Krankheit). Csépai, K., Endokrinologie, **11**: 260. 1932.

After studying subjects of Basedow's disease in the hospital for three days they were then started upon the first course of treatment consisting of the administration of a 5% solution of KI, 3 drops the first day and an increase of 1 drop every day until the pulse rate dropped and the nervous symptoms were improved (usually 10-15 drops per day). The dosage was now maintained at this level and on 2 consecutive days 220 R. units of x-ray were given in two fields over the neck, usually in front and behind. The KI medication was then decreased one drop a day until 3 drops was reached at which time it was discontinued for 2-3 weeks. The procedure was then repeated. Generally 6 treatment periods a year are given and one year's treatment is sufficient as a rule. In 40 patients reported 13 were cured, 21 improved, 2 unimproved, 2 died and 1 was worse after the treatment. The last 3 cases were all complicated by other conditions. Ages varied from 16 to 53. In one 36-year-old individual the basal metabolism dropped from 64% to 5% after four treatments. No contraindications are seen (except the nodular type of goitre) since surgery can be used if the patient does not respond.—R. A. Phillips.

The effect of feeding desiccated thyroid upon the sexual maturation of the albino rat. Da Costa, Esther and A. J. Carlson, Am. J. Physiol. **104**: 247. 1933.

Sixty female albino rats fed 0.5 to 1 mg. of desiccated thyroid daily showed a slight acceleration (calcium 215 days) in sexual maturation, while 41 fed 5 to 10 mg. of thyroid daily showed a retardation in pubescence (calcium 15 days). In several groups of male albino rats (3-9 animals each) fed 0.5 to 10 mg. of desiccated thyroid daily a decidedly lower relative weight of the testes than in the controls was the rule. This relationship was seen even when the body weight of the thyroid-fed rats was greater than that of the controls. In most cases the sexual maturation of the gonads of the male rat was depressed by thyroid feeding (0.5-10 mg. per day).—R. G. H.

Animal calorimetry; influence of phlorhizin glycosuria on the metabolism of dogs after thyroidectomy. Dann, M., W. H. Chambers and G. Lusk, J. Biol. Chem. **94**: 511. 1931.

The combined effect of thyroidectomy and phlorhizin on the metabolism of dogs was found to differ from that of phlorhizin alone in the following respects: (1) The increase in heat production usually observed after phlorhizin administration either did not occur or was very small when the thyroid had been removed. Three dogs whose basal heat outputs were 18.3, 11.8 and 11.9 calories per hour after thyroidectomy produced 20.2, 11.5 and 13.1 calories, respectively, when phlorhizinized, in contrast to a rise from 29 to 38 calories in a normal dog when phlorhizin was injected; (2) the increase in protein metabolism characteristic of the phlorhizinized animal was also partially or entirely abolished by previous thyroid removal. This was evident from the urinary nitrogen, which showed either no increase or an increase much smaller than that usually seen in phlorhizinized dogs. Ingested protein, however, exerted its usual specific dynamic action; (3) in two of the dogs, thyroidectomized and treated with phlorhizin, the D:N ratios were close to the Minkowski level of 2.8. In the third (an older series of experiments) the time required for "extra sugar" to be eliminated was longer than is usually the case in phlorhizin glycosuria. The amount of "extra sugar" was such that it could be accounted for by glycogen stored in the body rather than postulating its formation from fat. The respiratory quotients, which averaged 0.697, demonstrated that fat oxidation furnished the energy for the non-protein quota of the metabolism, and that the "extra sugar" could not have been derived from fat.
—M. Dann.

Relationship of thyroid disease to chronic nonspecific arthritis. Duncan, W. S., J. A. M. A. **99**: 1239. 1932. Abst., A. M. A.

The author calls attention to the fact that considerable divergence of opinion exists as to the etiology of the chronic nonspecific arthritis that occurs in thyrotoxicosis. It would appear that the abnormalities of the joints are not due to a specific toxin elaborated by the thyroid gland. Whether or not the individual in the presence of hyperthyroidism becomes sensitized to infection, which in a large proportion of instances has been found to be present, is a moot

question. It would appear logical to believe that such periarticular changes are the result of trophic disturbances initiated by the hyperactive thyroid gland through the vegetative nervous system. In conclusion, the author states that divergent manifestations of thyroid dysfunction are productive of articular disturbances that can be looked on as being characteristic of those altered physiologic states. Hyperthyroidism is accompanied by capsular and periarticular changes which, if inadequately treated, lead to an atrophic polyarthritis with characteristic contractures. These changes are highly amenable to well directed surgical measures on the thyroid. Articular manifestations of hypothyroidism are degenerative, are slowly progressive and are readily lessened in severity by the administration of thyroid extract in adequate dosage.

Some remarks concerning the histogenesis of the mammalian thyroid (Quelques remarques a propos de l'histogenesis de la glands thyroide des mammiferes). Florentin, P., Rev. franç. d'endocrinol. **9**: 12. 1931.

Histological examination of thyroids of a sexually mature hedgehog showed the left gland fully developed, the right in process of development. It appeared that vesicles develop from proliferation of walls of canals as diverticula of the original evagination. Differentiation and colloid formation is gradual; new vesicles may be formed from reserve embryonic tissue.—B. C.

The effect of arginine upon the body weight of mice injected with thyroxine, and bearing the tumor M63. Gilroy, E., Biochem. J. **25**: 414. 1931.

Experiments were carried out to determine whether a decreased rate of tumor growth under the influence of thyroxine was accompanied by loss of body weight in the host, and whether arginine could modify this effect. Mice (126) in which the tumor M63 had been implanted successfully were divided into groups, and injected with arginine or thyroxine, or both, 20 mice being kept as untreated controls. An indirect estimate of the body weight, exclusive of the tumor, was based on the assumption that if the tumor increased in size (caliper measurements), while total weight remained stationary, or decreased, some reduction in the body weight of the mouse must have occurred. Owing to the small numbers used no definite conclusion could be drawn, but the results suggested that thyroxine induced a loss of body weight, which did not occur when arginine was also injected. The relation of arginine to tumor growth and thyroid toxicity is discussed.—Author's Abst.

Therapeutic action of fluorides in exophthalmic goiter and hyperthyroidism: technic of fluoride treatment (Comment agiraient-ils thérapeutiquement les fluoreres dans le goître exophthalmique et dans l'hyperthyroidisme? Technique actuelle du traitement fluorique). Goldemberg, L., Semana méd. **39**: 1659. 1932. Abst., J. A. M. A. **99**: 869.

The author states that fluorides introduced in the organism (by either the oral or the intravenous route) have an action on the thyroid hormone by means of which this substance is neutralized or precipitated in the body fluids and tissues and its excessive production is arrested. The gradual diminution of the specific substance causes an amelioration of the clinical symptoms until the recovery of the patient is obtained. The oral administration, however, cannot be resorted to in all cases because some patients show gastro-intestinal disturbances. The author obtained good results with sodium fluoride given intravenously. The therapeutic action of the drug in exophthalmic goiter and hyperthyroidism is evident in a slow and gradual but continuous form. The nervous symptoms are the first to disappear after the first four or five injections. Sleep gradually returns. Tachycardia diminishes (except if the heart is already in a condition of hypersystole or asystole; but even in those cases digitalis therapy, which before the administration of sodium fluoride neither diminished the excessive rapidity of the action of the heart nor restored the tonus to the myocardium, recovers its cardiotonic action when its effects are combined with those of fluoride therapy). The basal metabolism slowly returns to normal or near normal. The size of the goiter diminishes gradually until it almost disappears. Exophthalmos greatly diminishes, although it does not disappear entirely and the tremor rapidly and completely disappears. The author begins the treatment with 2 or 3 cc. of a 2.5% solution of sodium fluoride in distilled water. The dose for the injection is gradually increased from 0.5 to 1 cc. in each injection. This dose is maintained until the amelioration of the clinical symptoms

begins to show. Then the dose is gradually diminished to 4 cc. per injection, which dose is maintained all through the series (from 15 to 20) of injections. At the beginning of the treatment the injections are given either every day or every other day. As soon as the thyrotoxic symptoms improve, the injections are given at intervals of three or four days. After the patient has received the first series of injections he is not given any more for 15 or 20 days, when another series of injections at the same interval is given. The series are thus given alternated with periods of rest for some months. Clinical cure, as a rule, appears between the fifth and tenth months of treatment. Some patients who support well the fluoride therapy by the oral route can receive the treatment in a combined form, that is, both by injections of the solution mentioned and by the oral administration of progressive doses of from 10 to 50 drops of a 2% solution of either ammonium or sodium fluoride, in milk, four times a day for 15 or 20 days. The author claims good results in cases in which antithyroid serum, iodide therapy and roentgen irradiation of the thyroid had previously failed. It seems advisable to continue the treatment for a minimal period of from five to six months and in some cases from 10 to 12 months; also to give the patient two or three series of injections every year for the two or three years following the first treatment. The treatment may also contribute in the preparation of the patients for operation in cases of hyperthyroidism with a large and sclerous goiter. Fluoride therapy, because of its neutralizing action on the thyroid hormone, seems to be able also to prevent postoperative thyrotoxicosis.

The effect of feeding desiccated thyroid gland on the flow of blood in the femoral artery of the dog. Herrick, J. F., H. E. Essex, F. C. Mann and E. J. Baldes, Am. J. Physiol. **105**: 434. 1933.

When the characteristic physiologic action of graduated doses of desiccated thyroid gland had been produced the flow of blood in the femoral artery of the dog (6 cases), as measured by the thermostromuhr method of Rein, was increased from 205 to 327%.—R. G. H.

Pituitary and thyroid; effect of anterior pituitary lobe extract on microscopical aspect of thyroid (Hipófisis y tiroides; acción del extracto del lóbulo anterior de la hipófisis sobre la histología de la tiroides del perro). Houssay, B. A., A. Biasotti and A. Magdalena, Rev. Soc. argent. de biol. **8**: 130. 1932.

Six puppies and 13 adult dogs received daily intraperitoneal injections of Evans and Simpson's (1931) anterior pituitary lobe extract, in doses of 10 cc. (3.4 gm. fresh gland). The right thyroid was removed in 22 normal dogs and afterwards at varying intervals the left thyroid was removed. Thirteen animals received in the interval between operations daily injections of pituitary extract. The same procedure was followed in 8 hypophysectomized dogs which also received pituitary treatment between the two thyroid operations. Dogs treated with extract for short periods showed resorption, liquefaction and vacuolization of colloid in areas or even in nearly all the gland. The height of the vesicular epithelium increased to 7-9 micra and even more (normal average found was 5.1 micra). In dogs treated for longer periods hypertrophy and hyperplasia were seen, even in the hypophysectomized animals. When treatment was discontinued in these last, 15 days later the thyroid again showed the typical atrophic aspect of the hypophysectomized dog. The left thyroid was removed and grafted into the kidney in 10 dogs; 5 received pituitary treatment. In all animals the grafts "took"; those injected had a typical hypertrophic reaction. The left thyroid was removed in 15 dogs, of which: (a) 5 received pituitary extract; (b) 5 pituitary extract and 3 gm. sheep thyroid per os daily; (c) 5 only thyroid powder. In series (a) a typical hypertrophy of the right thyroid followed; 3 animals in series (b) had no reaction, a slight one was observed in one case and a definite one in another. Animals in series (c) had a decrease in thyroid weight; the vesicles had increased diameter and low epithelium.

—J. T. L.

The thyroxine content of thyroglobulin. Jones, Mildred and B. O. Barnes, Proc. Am. Physiol. Soc. P. 58. 1933.

Harington and Randall estimated thyroxine in the thyroid gland by hydrolysis for 4 hours with sodium hydroxid and adjusting the pH to 5.0. They assumed that all the thyroxine was in the acid-insoluble fraction and that no

other form of iodine was present in this fraction. Leland and Foster have thrown doubt on the last assumption by showing that the acid-insoluble fraction yielded some acid-soluble iodine upon further hydrolysis. The latter authors hydrolyze for a longer time and extract the thyroxine with butyl alcohol. Using this method they found much less thyroxine in the thyroid. The authors have confirmed their method for extracting thyroxine. By a partial hydrolysis of thyroglobulin and bringing the pH to 5.0, the iodine was separated into acid-soluble and acid-insoluble fractions. When the method of Harington and Randall was applied to the acid-soluble fraction, as much as 20% of the iodine became acid-insoluble. The same fraction yielded considerable thyroxine by the method of Leland and Foster. It seems, therefore, that if hydrolysis is incomplete, adjusting the pH to 5.0 may not precipitate all the thyroxine. When both of the above methods were applied to four samples of hog thyroglobulin, the results were consistently much higher by the method of Harington and Randall. Analysis by the method of Leland and Foster yielded about 23% of the iodine in thyroxine combination.—Authors' Abst.

The effect of thyroidectomy and adrenalectomy on the basal metabolic rate of the rabbit (Le metabolisme basal chez le lapin thryroïdectomisé et surrénalectomisé et chez le lapin influencé par le traitement thyroïdien). Kaiwa, T., Tohoku J. Exper. Med. **19**: 96. 1932.

The basal metabolic rate in male rabbits, thyroidectomized and unilaterally or laterally adrenalectomized, showed a decrease of 21 to 40% from the normal. Thyroidectomy caused a decrease in the basal metabolic rate, but adrenalectomy, either unilateral or bilateral had no influence upon the basal metabolic and did not modify the effect of thyroidectomy upon metabolism.

—Author's Summary, Translated by M. O. L.

Congestive heart failure and hypertrophy in hyperthyroidism; a clinical and pathological study of 178 fatal cases. Kepler, E. J. and A. R. Barnes, Am. Heart J. **8**: 102. 1932. Abst., J. Nerv. & Ment. Dis. **77**: 418.

One hundred seventy-eight fatal cases of hyperthyroidism, consisting of 110 cases of exophthalmic goiter and 68 cases of hyperfunctioning adenomatous goiter, were studied. It was found that after excluding hypertension, syphilis and chronic disease of the valves of endocardium the weight of the heart exceeded Smith's maximal standard figures in 49% of the cases. In 12% of the cases the heart weighed less than 250 gm., in 22% it weighed between 250 and 300 gm., in 47% between 300 and 400 gm. and in 17% between 400 and 500 gm. In one case the heart weighed 530 gm. Thus, in a given case of hyperthyroidism the weight of the heart would depend on: (1) the weight of the heart before the onset of hyperthyroidism; (2) the age of the patient; (3) the duration of hyperthyroidism; (4) the amount of excess work for each beat as the result of hyperthyroidism; and (5) the amount and rapidity of the loss of body weight. Congestive heart failure occurred in 27 cases (15%) of the entire group of 178 cases. In 18 of these 27 cases hypertension or independent disease of the heart such as pericarditis, acute or chronic endocarditis, coronary sclerosis or syphilis was found to be present. In the remaining nine cases no cause for the congestive failure other than hyperthyroidism could be found.

A method of estimating the functional activity of the thyroid by means of urine or serum and studying the relationship between the thyroid and other endocrine organs. Koh, M. L., Korean M. J. **2**: 45. 1932. Abst., Chem. Absts. **26**: 5600.

The function of the thyroid is estimated quantitatively by means of an atropine-neutralizing substance, present in urine and the serum. This substance is determined by adding to the urine atropine sulfate solution, injecting into one eye of a cat, and comparing with the other eye as a control. If the pupil of the eye treated with the preparation is kept enlarged to from one and a half to twice the size of the control for ½-4 hours, no atropine-neutralizing substance exists in the urine being tested. When a rabbit is fed with powdered thyroid, 0.05 gm. per kgm. body weight daily for seven days, the atropine-neutralizing substance in the urine and serum increases; when the rabbit has been thyroidectomized, the atropine-neutralizing substance decreases markedly. If, however, a thyroid gland from another rabbit has been transplanted into the thyroidectomized rabbit, or if thyroxine or extract of thyroid has been in-

jected into the thyroidectomized animal, the atropine-neutralizing substance previously absent reappears transitorily. The atropine-neutralizing substance is not thyroid hormone itself, since after thyroidectomy the substance increases slightly in about 10 days. It is believed to be a substance that increases or decreases proportionately with the quantitative changes of the thyroid hormone by which it is controlled. The substance is easily soluble in water, but not in alcohol or ether. It is stable up to 80° for 30 minutes, but is destroyed at 100°. In serum it exists combined with albumin, and cannot be separated, even by adsorption with siliceous earth.

The treatment of eclampsia and pre-eclampsia with thyroxine (Zur Thyroxinbehandlung der Eklampsie und der präeklomptischen Störungen). Küstner, H., Klin. Wchnschr. **11:** 1016. 1932. Abst., Am. J. M. Sc. **186:** 298.

The author and others claim that in eclampsia there is an increased activity of the hypophysis, with an increased production of posterior lobe hormone. Although evidence is available that thyroid function is also increased, as a result of the overactivity and antagonistic effect of the posterior lobe pituitary the balance is dominated by the latter. This concept suggests that the use of thyroxine in eclampsia is rational. The author administered thyroxine in 48 cases of eclampsia. The daily dose varied usually between 2 and 3 mg. by mouth. The total amount administered also showed considerable variations. One patient received 8 mg.; another, 48 mg. In 26 cases, the author claims an improvement due to thyroxine. The improvement manifested itself either in the cessation of convulsions or in decrease of the edema. In 18 cases the improvement was not definite. One patient died. None of the cases with marked improvement had an arterial pressure over 180 mm. Hg. systolic pressure; but the edema in this group was usually of marked degree. The group with no improvement, on the other hand, exhibited a relatively higher systolic arterial pressure (180 to 230 mm. Hg.) and slight edema only. Cases with pre-eclamptic manifestations showed particularly marked improvement. The author does not advocate thyroxine therapy alone, but states that in some cases it may be of great benefit. Even relatively large doses of thyroxine failed to exert obvious harmful effects on the mother or on the fetus.

The condition of the vegetative nervous system in exophthalmic goiter and in the Basedowoid sympathetic syndrome (L'etat du système neurovégétatif dans la maladie de Basedow et dans le syndrome sympathique basedowiforme). Labbé, M., E. Azérad and E. Solomon, Ann. d. méd. **29:** 271. 1931. Abst., Arch. Neurol. & Psychiat. **27:** 1483.

Exophthalmic goiter is a combination of two different syndromes: (1) hyperthyroidism, and (2) a disturbed balance of the sympathico-vagus systems with predominance of sympathetic excitability. Both syndromes may occur isolated; in the first case in the form of goiter with hyperthyroidism, in the second case in the form of the "basedowiform" syndrome. The classic test for the demonstration of hyperthyroidism is the determination of the basal metabolic rate. The Goetsch test and the oculocardiac tests, however, devised for the examination of sympathetic and vagus functions, do not always give uniform results. The following method was described to determine the degree of excitability of the vagus; the patient rests on a couch and his pulse rate is counted; the number obtained is an expression of the "relative tonus," the equilibrium between sympathetic and vagus regulation of the heart. Then 0.5 mg. of atropine is injected intravenously. The pulse rate is increased after injection, still more so if the patient stands erect (orthostatic reaction). After lying down again, the pulse becomes slower. If the rate is approximately the same as it was before the patient stood up, the experiment is finished. If, however, the pulse rate is rapidly diminished again, the paralysis of the vagus has not been complete. Another 0.25, 0.3 and, finally, 0.75 mg. of atropine are injected at short intervals, until the patient's pulse rate does not slow down below the rate observed after the injection. The rate in the prone position is indicative of the "absolute tonus" of the sympathetic; the difference between the value for the latter and the pulse rate before the injection indicates the "vagus tonus." According to Danielopolu, the following rates are averages for normal persons: relative tonus, 72; absolute vagus tonus, 52 (from 48 to 58); absolute sympathetic tonus, 124 (from 116 to 128). Of nine cases of exophthalmic goiter an increased irritability of vagus and sympathetic (amphotonia) was found in seven. Relative tonus from 88 to 120; absolute vagus tonus from

44 to 72; absolutely sympathetic tonus from 104 to 188. From 1.25 to 1.75 mg. of atropine was used. In three cases of toxic adenoma, the corresponding figures were: from 80 to 88; from 24 to 48, and from 112 to 132. In the first group the oculocardiac test was normal in three cases; in three other cases the pulse rate was reduced during compression of the eyes.

Fate of the thyroid hormone in experimental hyperthyroidism. Mathieu, F. and B. O. Barnes, Am. J. Physiol. **101:** 75. 1932.

Since reports had been made that thyroxine was excreted largely through the gall bladder, this study was undertaken to see if the excreted compound was still active. Six dogs were fed thyroid and the bile collected. The bile was then administered to other dogs which were trained for basal metabolism tests. No increase in basal rate was obtained. The iodine content of this bile was found to be low. The experiment is being repeated, using thyroxine instead of desiccated thyroid. Urinary studies are also under way.—Authors' Abst.

Constitution of 3254 Freiburg students, including the size of thyroid gland (Ergebnisse der Untersuchungen an 3254 Feiburger Studenten). Meyer, E., Ztschr. f. Konstitutionsechre. **16:** 448. 1932.

Half of the students from the region of Baden have enlarged thyroids, while only 20% of those from other regions showed such enlargement.—A. T. R.

Phychogenic factors and psychotherapy in hyperthyreosis and rapid heart imbalance. Mittelmann, B., J. Nerv. & Ment. Dis. **77:** 465. 1933.

The author studied 60 patients presenting Graves' Syndrome (with basal metabolic rate above plus 20) to determine the importance and scope of psychogenic factors in this disease entity. It is concluded that the presence of a psychogenic factor in the great majority of patients studied is proved by the following facts: (1) There is a very close time relation between the psychic trauma in the patient's history and the onset of the first symptoms of hyperthyroidism. The first symptom of Graves' disease in clear-cut cases is a "nervousness," that is, motor restlessness, irritability, which can be differentiated, both by the examiner and the patient, from related neurotic symptoms. The interval between the psychic trauma and the patient's awareness of a new symptom is hardly ever longer than a week or two. A latency period hardly exists. (2) During the interview, when the psychic trauma is touched on, the patient shows all signs of the tremendous reaction which he has had to the previously mentioned trauma at the time of its occurrence (embarrassment, weeping, flushing, confusion, etc.). (3) The sensitization to this psychic trauma can be traced to neurotic infantile relationships, the discussion of which produces in the patient a reaction similar to the one mentioned above. By sensitization is meant an increased responsiveness to specific stimuli, and an inability to cope successfully with those responses. The psychic sensitization, and the psychic mechanism of precipitation of Graves' Syndrome seems near to that of hysteria. Of the 60 patients, five did not show psychogenic factors. Phychotherapy consists in giving the patient such insight as possible into his emotional life, and also in attempting to influence the environment favorably. Psychotherapy serves two purposes: one, the relief of symptoms which are directly due to the patient's neurotic attitude; two, the prevention of recurrence of Graves' Syndrome, or its cure in the active stage. Many patients have relapses due to similar psychic traumata. The patients are to be "desensitized" against the psychic trauma that produced the first attack. Psychotherapy should always be combined with either surgery, medical management, or x-ray treatment. It is emphasized that the study concerned only the psychic aspect of Graves' Syndrome. The constitutional somatic background requires further study.

—Author's Abst.

Experimental study of thyroid function during pregnancy, parturition and puerperium; on metabolism of iodine during pregnancy, parturition and puerperium. Nakamura, U., Jap. J. Obst. & Gynec. **15:** 114. 1932. Abst., J. A. M. A. **99:** 1984.

The author states that in the normal rabbit that rate of discharge of the given iodine, the required hours and the process show a considerable marked individual variation. If examined by repeating on the normal rabbit, the rate

of the discharge and the process resemble each other in the same rabbit. The extirpation of the thyroids causes delay of discharge, decrease of the rate in the early stage and a slight increase of the rate of the whole discharged in from one to two weeks after the operation; but in from five to seven weeks after it the rate and the process are approximate to those before the operation. Feeding of thyroid accelerates the discharge of iodine into the urine and causes an increase of the discharge in the early stage, a decrease in the later stage, shortening of the hours required for the discharge, and an increase of the total amount discharged. In the earlier period of pregnancy the iodine discharge into the urine is markedly accelerated and the rate of the total discharge slightly increases. The hours required for discharge are shortened. In the latter period of pregnancy the iodine discharge into the urine is accelerated, but the rate of the total discharge decreases. A shortening is observed in the hours required for discharge. It may be considered that the acceleration of the discharge of the dosed iodine into the urine is due to the hyperfunctioning of the thyroids.

Metabolic studies on the site of action of the thyroid (Stoffwechseluntersuchungen zur Frage des Angriffspunktes der Schilddrüsensubstanz). Oberdisse, K., Arch. f. exper. Path. u. Pharmakol. **162:** 150. 1931. Abst., Chem. Absts. **26:** 3577.

The increased metabolism caused by injecting thyroxine subcutaneously into rats is not affected by sectioning the spinal cord at the thoracic level, indicating that it acts directly upon the cells, rather than through the central nervous system. There is a roughly quantitative relationship between the amount injected and the metabolic effect. There was no evidence that the organism builds a protective tolerance after a single injection, a second injection 48 days later proving equally effective.

Studies on the Reid-Hunt reaction. IV. The dependence of the content of active substance in the thyroid glands upon alimentary and hormonal factors (Untersuchungen mit der Reid Huntschen Reaktion; die Abhängigkeit des Wirkstoffgehaltes der Schildrüse von alimentären und hormonalen Faktoren). Paal, H. and W. Huber, Arch. f. exper. Path. u. Pharmakol. **162:** 521. 1932. Abst., Chem. Absts. **26:** 2227.

Increasing the carbohydrate and protein content of the diet causes as much as a 100% increase in the hormonal content of the thyroid gland in rats, as measured by the Reid-Hunt reaction. Inorganic iodine has little effect. Thyronine, yatren, diiodotyrosine and thyroxine cause an increase in the order named. Insulin depresses the hormonal content. Prehormone (derived from the anterior pituitary lobe) acts like thyroxine, because of its content of hormothyrine. Prolan, which contains no hormothyrine, is inactive.

Observation of Morch's method for standardization of thyroid gland preparation. Palmer, W. W. and J. P. Leland, Proc. Soc. Exper. Biol. & Med. **29:** 1195. 1932.

Attempts to use the CO_2 output in mice as recommended by Morch in biological assay of thyroid gland preparation proved unsatisfactory on account of the great variation of results on nine different glands and 38 experiments. The method is long and tedious.—W. W. Palmer.

Physico-chemical changes in plasma of thyroidectomized dogs (Modificaciones fisicoquímicas del plasma de los perros tiroprivos). Rossignoli, J. J., E. di Benedetto, I. Guerrrero and E. J. di Benedetto, Rev. Soc. argent. de biol. **8:** 213. 1932.

Viscosity determined by Ostwald's viscosimeter kept at constant temperature (37° C. $\pm$ 0.01° C.) was found to increase after operation (average increase 12%). Plasma proteins increased slightly (11%) as determined by the micro-Kjedahl and nesslerization method; globulins always increased considerably (28%). The albumin: globulin ratio was markedly diminished. Nonprotein nitrogen increased 25%. Alkaline reserve (van Slyke's gasometric method) gave slight increases in some cases. The pH (Michaelis' technique) showed no variation in the 3 experiments in which it was determined. Bovine thyroid powder given per os reversed these modifications, especially the globulin

value which returned to the normal figure or below. The most characteristic change after thyroidectomy was increase in globulins, which produced and increased the viscosity. In hyperthyroidism the contrary changes occurred.
—J. T. L.

Influence of thyroxine on cholesterolemia and lipemia (Influence de la thyroxine sur la cholesterolemie et la lipemie). Parhon, C. I. and I. Ornstein, Compt. rend. Soc. de biol. **108:** 303. 1931.

The authors report the effect of giving thyroxine on the cholesterol, fatty acids and total fats in five cases. The cholesterol values before and after treatment were: 195-160 mg., 246-170 mg., 225-182 mg., 170-150 mg., 193-170 mg. The total fat values were: 425-400 mg., 950-500 mg., 815-560 mg., 540-396 mg., 800-504 mg. They conclude that treatment with thyroxine, especially in the form of intramuscular injections, diminishes the cholesterolemia and likewise the amount of fatty acids and total fats, and can be used as a preventive against arteriorsclerosis.—J. M. Looney.

The diagnosis and treatment of atypical hyperthyroidism. Rankin, F. W. and S. F. Haines, Northwest Med. **31:** 549. 1932.

Technical considerations of the greatest importance are: (1) Avoidance of injury to the recurrent laryngeal nerves; (2) efficient hemostasis; (3) avoidance of injury to the parathyroid bodies; (4) preservation of sufficient thyroid tissue to maintain metabolic processes within normal limits, and (5) satisfactory cosmetic considerations.—F. W. Rankin.

Standardization of thyroid preparations (Zur Standardisierung von Thyreoideapräparaten). Rotter, G. and M. Mecz, Arch. f. exper Path. u. Pharmakol. **166:** 649. 1932. Abst., Physiol. Absts. **18:** 204.

In a series of commercial thyroid preparations the total iodine, thyroxine iodine, and inorganic iodine were estimated by Harington's method and compared with the results of biological standardization by the methods of Kreitman and Nobel. The thyroxine iodine values and the biological standardization gave parallel results. It is therefore recommended that thyroid preparations be standardized to contain $0.10 \pm 0.01\%$ thyroxine iodine by Harington's method, while the inorganic iodine should not exceed 10% of the total iodine. Pig thyroid has a lower thyroxine content, both in the fresh and dried state, than horse or ox thyroid. Albino guinea-pigs are hypersensitive to thyroid.

The mitogenetic rays of the blood in artificial hyperthyroidism and Basedow's disease (Die mitogenetische Strahlung des Blutes bei künstlicher Hyperthyreose und bei Basedowscher Krankheit). Samarajew, W. N., Endokrinologie, **11:** 335. 1932.

This paper, the third of a series, attempts to ascertain the cause of the increase of the mitogenetic rays in the blood of metamorphosing amphibians. The blood of pigeons fed Thyreoidin and humans with Basedow's disease was studied. The mitogenetic ray content of the bood was followed by the rate of budding of yeast cells exposed to the blood. The exposure times were 1, 3, 5 and 10 minues. Control blood showed an increasing rate of induction of budding, as the time progressed. The blood of the experimental subjects showed an increase of the induction process up to 5 minutes and then at 10 minutes a return to the three-minute rate.—R. A. Phillips.

Therapeutic experiments with hypophyseal hormone influencing thyroid (Therapeutische Versuche mit thyreotropem Hormon). Schittenhelm, A. and B. Eisler, Klin. Wchnschr. **11:** 1783. 1932. Abst., J. A. M. A. **99:** 2299.

The authors after referring to former investigations in which they demonstrated that there is a hypophyseal hormone that stimulates the activity of the thyroid, now relate their clinical experiences with this hormone. In myxedema they noted a considerable increase in the iodine content of the blood, but the basal metabolism remained unchanged. The clinical aspects of myxedema remained uninfluenced by the hormone. In a case of congenital imbecility with abnormal thyroidal action, the iodine content of the blood increased under the influence of the hormone but there was no fundamental change in the clinical condition. In obesity the action of the hormone is weaker than that of thy-

roxine, but it was possible to reduce the body weight by means of the hormone without causing complications. The subcutaneously injected dose of the hormone is from 600 to 1,000 guinea-pig units a day.

Hypermotility of the gastro-intestinal tract in hyperthyroidism; a study of 42 cases. Shirer, J. W., Am. J. M. Sc. **186**: 73. 1933.

The study of a series of 42 patients with hyperthyroidism showed that hypermotility of the gastro-intestinal canal occurs in this condition but that the degree of hypermotility is not an index to the severity of the disease. Hypermotility of the gastro-intestinal tract was decreased, usually markedly, after removal of the thyroid in 76% of the cases studied. Hypermotility and anacidity occurred concomitantly in 12 cases of hyperthyroidism in this series. —Author's Summary.

Malignant goitres (Bocios cancerosos). Solá, E., Septima Reunión Soc. Argentina Patol. Reg. Norte, **1**: 148. 1932.

Malignant goiters are rarely reported from North Argentina, perhaps because of diagnostic difficulties. Solá reports four cases that he encountered in a single year, all in women. The malignant condition developed in each case in an old goiter. Each patient had hereditary or acquired lues that had been neglected. Two presented anamnestic evidence of hepatic or biliary involvement. All the goiters were of great size, one (18x24 cm.) being the largest in the world literature.—Author's Summary, Abbreviated.

The basal oxygen consumption of goitrous and nongoitrous rats. Spence, A. W., Brit. J. Exper. Path. **13**: 149. 1932. Abst., Chem. Absts. **26**: 4093.

Simple goiter was produced in the majority of 24 young rats fed on a vitamin-deficient diet. Determinations of the basal oxygen consumption were made at two or three-month intervals on the 24 experimental animals and on six normal controls of the same age. A series of determinations on the normal rats over a period of 12 months showed that when the animals were two months old and were gaining rapidly in weight this oxygen consumption was high, but when they reached the age of 4.5 months and their rate of growth was diminished, their oxygen consumption fell considerably and maintained a fairly constant level for the rest of their lives. The basal oxygen consumption of normal rats, which were gaining in weight, was more nearly proportional to their body surface than to their weight. The findings in the rats fed on a vitamin-deficient diet were liable to variations due to the prevalence of secondary infections. The majority showed no significant alternation in basal oxygen consumption which would point to a definite thyroid disorder. Four goitrous animals, however, showed a fall in oxygen consumption below normal after nine months.

The effect of rachitogenic diets on the thyroid gland of the albino rat. Juanita Thompson, J. Nutrition, **5**: 359. 1932.

This study was based on an examination of the thyroid glands from 385 rats. Diffuse hyperplasia was produced in rats through the feeding of the Steenboch rachitogenic diet or its various modifications. Hyperplasia developed in the presence or absence of the antirachitic vitamin. The factor underlying the development of hyperplasia in the experimental animals on these diets was a deficiency of iodine, associated with an excessive amount of calcium carbonate. Increasing the amount of calcium carbonate in diets deficient in iodine resulted in enhancement of the degree of hyperplasia. Variations in the degree of hyperplasia were found within similar experimental groups. The addition of a small amount of potassium iodide to the diets prevented the development of hyperplastic processes.—Author's Abst.